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Review Article

A concise review on analytical profile of risperidone

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ABSTRACT

Risperidone (RIS) is an atypical antipsychotic medication. This works by selectively antagonising serotonin 5HT2 and dopamine D2 receptors. It's used to treat schizophrenia and other mental illnesses. As per literature, RIS was first approved USA by Food and drug administration (FDA) in 1993. Therefore, the main objective of this analysis of RIS in pharmaceutical and biological formulation is in both qualitative and quantitative terms. In this review article, we have summarized UV/Vis spectroscopy, high-performance liquid chromatography (HPLC), High-performance thin-layer chromatography (HPTLC), Liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS) etc. based methods for estimation of risperidone. In addition to that, we have discussed the bioanalytical methods for RIS analysis. In conclusion, this review article will help to research scholars for further method development for drug estimation in pharmaceutical dosage forms and biological fluids.

1. Introduction

Risperidone is a second-generation antipsychotic (SGA) medicine that is used to treat a variety of mood and mental health disorders, such as schizophrenia and bipolar disorder. It's one of the most popular SGAs.[1] An excess of dopaminergic D2 and serotonergic 5-HT2A activity is hypothesised to induce schizophrenia and different mood disorders, resulting in over activity of central mesolimbic and mesocortical pathways, respectively. Risperidone inhibits dopaminergic D2 receptors and serotonergic 5-HT2A receptors in the brain, which is considered to lessen over activity.[1]

Risperidone is a benzisoxazole derivative with antipsychotic property. Risperidone (RIS) chemically known as 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidine-4-one.[2,3] Figure 1 depicts the chemical structure of RIS.

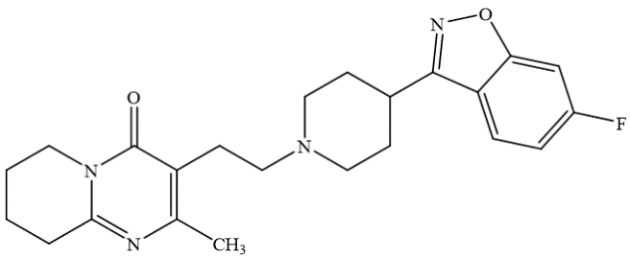

Fig. 1: Chemical structure of RIS

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1.1. Mechanism of action

Risperidone binds to a variety of receptors, including 5-HT2A/2C serotonin receptors, D2 dopamine receptors, and alpha 1 and H1 receptors. It has no discernible effect on M1 receptors. At D2 and 5-HT2A receptors, its major metabolite (9-hydroxyrisperidone) is almost equal to the parent molecule.[2]

1.2. Pharmacokinetics

1.2.1. Absorption

Well taken in. Risperidone has a 70% absolute oral bioavailability (CV=25%). When compared to a solution, the relative oral bioavailability of risperidone from a tablet is 94% (CV=10%).[1]

1.2.2. Distribution

The volume of distribution of risperidone is approximately 1 to 2 L/kg.[1]

1.2.3. Metabolism

Hepatic cytochrome P450 2D6 isozyme metabolises it to 9-hydroxyrisperidone, which has a similar receptor binding affinity as risperidone. N-dealkylation occurs to a lower amount in risperidone.[2]

1.2.4. Elimination

Risperidone is processed extensively in the liver. Renal clearance of both risperidone and 9-hydroxyrisperidone was reduced in healthy senior adults, and elimination half-lives were longer than in young healthy subjects.[2]

1.2.5. Pharmacodynamics

Risperidone's main effect is to reduce dopaminergic and serotonergic pathway activity in the brain, which helps to alleviate symptoms of schizophrenia and mood disorders.[1]

2. Analytical Account of RIS

For the determination of RIS in bulk and pharmaceutical formulations, an exhaustive literature search found numerous analytical techniques such as UV/Visible Spectrophotometry, HPLC, HPTLC, LC-MS/MS, and bioanalytical approaches. RIS is measured as a single constituent and in combination with Fluoxetine, Olanzapine, Clozapine, Ziprasidone, Haloperidol in various dosage forms and 9-hydroxyrisperidone its active metabolites forms. Figure 2 shows different analytical methods implemented for the estimation of RIS.

2.1. Bio-analytical method for RIS

Bio-analysis is a sub-discipline of analytical chemistry covering the quantitative measurement of xenobiotics (drugs and their metabolites, and biological molecules in unnatural locations or concentrations) and biotics (macromolecules, proteins, DNA, large molecule drugs, metabolites) in biological systems.[4] The summary of the reported bioanalytical methods is shown in Table 1.

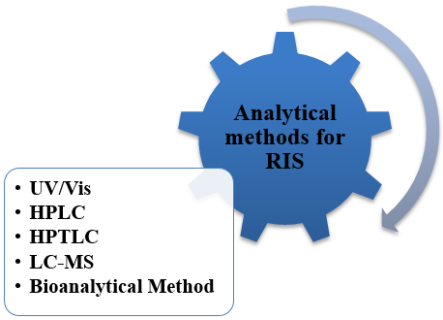

Fig. 2: Analytical methods of RIS

2.2. UV-Visible spectroscopy method for RIS

To date, lots of spectrophotometric methods have been accounted for the determination of RIS alone. This review compiles three papers describing spectrophotometric methods for determination of alone RIS. The details of Spectrophotometry determination of basic principle, sample matrix, lambda max, solvent linearity range and the correlation coefficient are summarized in Table 2.

2.3. HPLC method for RIS

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision, and accuracy are attainable only if wide-ranging system suitability tests are carried before the HPLC analysis. For this reason, the expense to be paid for the high specificity, precision, and accuracy is also high.[25] The summary of the reported HPLC methods is shown in Table 3.

2.4. HPTLC method for RIS

Thin-layer chromatography is a popular technique for the analysis of a wide variety of organic and inorganic materials, because of its distinctive advantages such as minimal sample clean-up, a wide choice of mobile phases, flexibility in sample distinction, high sample loading capacity and low cost. *R. B. Patel et. al* established HPTLC method development and validation for analysis of risperidone in formulation and in-vitro release study. TLC was carried out by stationary phase silica gel 60 F_{254} plates with methanol-ethyl acetate 8.0:2.0 (v/v) as mobile phase. The linearity range for risperidone was 100-600 ng per band. The developed method was successfully applied for determination of risperidone in formulation.[34]

Table 1: Bio analytical determination of RIS

Sr. No.	Drug	Sample Matrix	Method	Column	Detection	Internal Standard	Ref.
1	RIS	Human plasma	HPLC	Nucleosil C8 column	280 nm	Diltiazem	5
2	RIS	Plasma	HPLC	Cyano column	***	Remoxipride	6
3	RIS	Human plasma	HPLC-DAD	C8 column	240 nm	Clozapine and Loxapine	7
4	RIS	Human plasma	HPLC-MS/MS	Alltima-C18 Column	***	Paroxetine	8
5	RIS	Human plasma	HPLC	Waters XTerra RP-18 column	278 nm	Clozapine	9
6	RIS	Human plasma & saliva	LC	Reversed phase C18 column	***	Pipamperone	10
7	RIS	Human plasma	LC/MS/MS	Betasil C18 column	***	Methyl risperidone	11
8	RIS	Human plasma	LC–MS/MS	Analytical column	***	Acetonitrile	12
9	RIS	Rat plasma	UPLC-MS/MS	BEH C18	***	Propranolol	13
10	RIS & 9-HRIS	Human Serum	HPLC	ODS Hypersil C18	285 nm	Clozapine	14
11	RIS & 9-HRIS	Human plasma	LC–MS-MS	Atlantis HILIC Silica C18 column	***	Clozapine	15
12	RIS & 9-HRIS	Human plasma & urine	LC–MS/MS	Chiralcel OJ column	***	Methanol	16
13	RIS & 9-HRIS	Human plasma, urine & saliva	MEPS-LC-UV	C8 reversed-phase column	238 nm	Diphenhydramine	17
14	RIS & 9-HRIS	Human plasma	DLLME-LC-MS/MS	Ascentis® Express C18 chromatographic column	***	Clozapine	18
15	RIS & 9-HRIS	Plasma	LC-MS/MS	C18 column	***	Clozapine	19
16	RIS, FLX & 9-HRIS	Rat plasma	UPLC-MS/MS	ACQUITY UPLC BEH C18 column	***	Olanzapine	20
17	OLZ, RIS, 9-HRIS, CLZ, HAL & ZIP	Rat plasma	LC/ESI-MS/MS	Waters Atlantis™ dC-18	***	Midazolam	21

***Not provided

Table 2: Spectrophotometric methods used for determination of RIS

Sr. No.	Drug	Matrix	Solvent	Lambda Max (nm)	Linearity (μg/mL)	Correlation coefficient (R^2)	Ref.
1.	RIS	Pure form & pharmaceutical dosage forms	Methanol	240 and 280 nm	20 to 60 μg/ml	0.99	22
2.	RIS	Bulk &Tablets Formulation	0.1N HCl	238 nm	2-12 μg/ml	0.999	23
3.	RIS	Bulk drug & Pharmaceutical formulation	0.1N HCL	280 nm	2 to 6 μg/ml	0.99	24

Table 3: Summary of HPLC methods for the determination of RIS in a single and combined dosage form

Sr. No.	Drug name	Column	Mobile phase	Lambda max (nm)	Linearity (μg/mL)	Retention time (min)	Flow rate (mL/min)	Detector	Ref.
1.	RIS	C18 column	Acetonitrile-potassium dihydrogen phosphate (45:55, v/v, pH 6.5; 0.05 M)	237 nm	1–100 μg/mL	6 min	1.0 mL/min	PDA	26
2.	RIS	C18 column	Methanol: acetonitrile (80 : 20, v/v)	280 nm	10–60 μg/mL	3.35 ± 0.01	1 mL/min	PDA	27
3.	RIS	Hypersil ODS C-18 column	Methanol-acetonitrile-phosphate buffer (0.02 M) (65 : 20 : 15, v/v/v)	238 nm	1.0–10 mg/ml-1	6.16 min	1.0 ml/min-1	***	28
4.	RIS	Waters Xterra RP8 column	(10 mM potassium dihydrogen phosphate, pH 3.5± 0.05): acetonitrile: methanol (65:20:15)	276 nm	5-45 μg/mL	12 min	1.0 mL/min	UV	29
5.	RIS	Gemini C-18	Methanol: acetonitrile: 50 mM potassium dihydrogen orthophosphate (80:10:10 v/v)	234 nm	1-11 μg/ml	2.5 min	1.3 ml/min	UV/VIS	30
6.	RIS	Lichrosorb RP C 18 column	Methanol:0.05M potassium dihydrogen phosphate pH 7 (65:35 (v/v))	280 nm	25–500 μg/ml−1	***	1 ml/min−1	DAD	31
7.	RIS	Purosphere STAR RP-18e	Water: glacial acetic acid 0.50 %: triethylamine 0.80 %: acetonitrile (65.00: 0.32: 0.52: 34.16, v/v)	294 nm	25.00 μg/mL to 250.00 μg/mL	***	1 mL/min	DAD	32
8.	RIS & HPD	XBridge C18	Methanol: triethyl amine Buffer (60::40) and the pH of triethylamine adjusted to pH2.5 using orthophosphoric acid	260 nm	2-10 μg/ml & 8-40 μg/ml	1.82 min & 4.42 min	1.0 ml/min	PDA	33

***Not provided

3. Conclusion

The present review article provides comprehensive data of various analytical and bioanalytical methods developed for RIS alone and in combinations. For analysis purpose, different analytical methods have been reported that includes HPLC, HPTLC, UV spectroscopy, LC-MS/MS etc. The method along with their details concerning the mobile phase, stationary phase, retention time, etc., have been summarized in tabular form that will more helpful for the researchers for further analytical m3ethod development for estimation of RIS in dosage form and pure form. In the future, enlisted data can be used for the development of analytical methods bio-analysis of RIS in pharmaceutical and biological formulations. Finally, it presents an opportunity for greater information on what has already been done and what new methods and changes can be developed to get a better estimation of RIS.

4. Abbreviations

1. RIS - Risperidone
2. USA — United states of America
3. DA — Food and drug administration
4. UV/VIS - Ultra violet/visible spectroscopy
5. HPLC — High-performance liquid chromatography
6. HPTLC — High-performance thin layer chromatography
7. LC-MS/MS — Liquid chromatography-mass spectroscopy-mass spectroscopy
8. SGA — Second-generation antipsychotic
9. DNA — Deoxyribonucleic acid
10. RP — Reverse phase
11. nm — Nanometer
12. μg/mL — Micro gram per Milliliter
13. PDA - Photo diode array
14. TLC — Thin layer chromatography

5. Source of Funding

None.

6. Conflict of Interest

None.

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References

1. Risperidone is a second-generation antipsychotic medication used to treat a number of mental health disorders including schizophrenia, bipolar mania, psychosis, or as an adjunct in severe depression. Available from: http://go.drugbank.com/drugs/DB00734.
2. Risperidone; 2021. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Risperidone.
3. Risperidone; 2022. Available from: https://en.m.wikipedia.org/wiki/Risperidone.
4. Spooner N. Dried blood spot sampling for quantitative bioanalysis, time for a revolution. *Bioanalysis*. 2010;2(11):1781. doi:10.4155/bio.10.153.
5. Foroutan SM, Zarghi A, Shafaati A. Rapid high performance liquid chromatographic determination of risperidone in human plasma. *Iran J Pharm Res*. 2010;5(1):37–70. doi:10.22037/IJPR.2010.650.
6. Aravagiri M, Marder SR, Putten TV, Midha KK. Determination of risperidone in plasma by high-performance liquid chromatography with electrochemical detection: application to therapeutic drug monitoring in schizophrenic patients. *J Pharm Sci*. 1993;82(5):447–9. doi:10.1002/jps.2600820503.
7. Raggi MA, Bugamelli F, Sabbioni C, Saracino MA, Petio C. HPLC-DAD determination of plasma levels of the antipsychotic risperidone and its main metabolite for toxicological purposes. *J Separation Sci*. 2005;28(3):245–50. doi:10.1002/jssc.200401939.
8. Huang MZ, Shentu JZ, Chen JC, Liu J, Zhou HL. Determination of risperidone in human plasma by HPLC-MS/MS and its application to a pharmacokinetic study in Chinese volunteers. *J Zhejiang Univ Sci B*. 2008;9(2):114–20. doi:10.1631/jzus.B0710439.
9. Vergara PT, Sepulveda J, Plessing CV. Pharmacokinetic study of risperidone: application of a hplc method with solid phase extraction. *J Chilean Chem Soc*. 2011;56(1):606–9. doi:10.4067/S0717-97072011000100019.
10. Saracino MA, De Palma A, Boncompagni G, Raggi MA. Analysis of risperidone and its metabolite in plasma and saliva by LC with coulometric detection and a novel MEPS procedure. *Talanta*. 2010;81(4-5):1547–53. doi:10.1016/j.talanta.2010.02.067.
11. Bhatt J, Subbaiah G, Singh S. Liquid chromatography/tandem mass spectrometry method for the simultaneous determination of olanzapine, risperidone, 9-hydroxyrisperidone, clozapine, haloperidol and ziprasidone in rat plasma. *Rapid Commun Mass Spectrom*. 2006;20(6):2109–14. Available from: https://doi.org/10.1002/rcm.2537. doi:10.1002/rcm.2914.
12. Kousoulos C, Dotsikas Y, Loukas YL. Turbulent flow and ternary column-switching on-line clean-up system for high-throughput quantification of risperidone and its main metabolite in plasma by LC-MS/MS: application to a bioequivalence study. *Talanta*. 2007;72(2):360–7. doi:10.1016/j.talanta.2006.10.049.
13. Rub RA, Beg S, Kazmi I, Afzal O, Almalki WH, Alghamdi S, et al. & Ahmed FJ. Systematic development of a bioanalytical UPLC-MS/MS method for estimation of risperidone and its active metabolite in long-acting microsphere formulation in rat plasma. *J Chromatography B*. 2020;1160:122433. doi:10.1016/j.jchromb.2020.122433.
14. Kirschbaum KM, Finger S, Vogel F, Burger R, Gerlach M, Riederer P, et al. LC with column-switching and spectrophotometric detection for determination of risperidone and 9-hydroxyrisperidone in human serum. *Chromatographia*. 2008;67(3):321–4. doi:10.1365/s10337-007-0506-1.
15. Zhang X, Zhao X, Zhang C, Yang L, Xiong X, Zhou Y, et al. Validation of an LC-MS-MS method for the determination of risperidone and 9-hydroxyrisperidone in human plasma. *Chromatographia*. 2010;71(11):1015–23. doi:10.1016/j.jchromb.2008.04.041.
16. De Meulder M, Remmerie BM, De Vries R, Sips LL, Boom S, Hooijschuur EW, et al. & Timmerman PM. Validated LC-MS/MS methods for the determination of risperidone and the enantiomers of 9-hydroxyrisperidone in human plasma and urine. *J Chromatography B*. 2008;870(1):8–16. doi:10.1016/j.jchromb.2008.04.041.
17. Mandrioli R, Mercolini L, Lateana D, Boncompagni G, Raggi MA. Analysis of risperidone and 9-hydroxyrisperidone in human plasma, urine and saliva by MEPS-LC-UV. *J Chromatography B*. 2011;879(2):167–73. doi:10.1016/j.jchromb.2010.11.033.
18. Alcantara G, Calixto LA, Rocha BA, Júnior FB, De Oliveira A, De Gaitani CM, et al. A fast DLLME-LC-MS/MS method for risperidone and its metabolite 9-hydroxyrisperidone determination in plasma samples for therapeutic drug monitoring of patients. *Microchem J*. 2020;156(1):104894.

19. Vanwong N, Prommas S, Puangpetch A, Hongkaew Y, Nuntamool N, Nakorn CN, et al. Development and validation of liquid chromatography/tandem mass spectrometry analysis for therapeutic drug monitoring of risperidone and 9-hydroxyrisperidone in pediatric patients with autism spectrum disorders. *J Clin Lab Anal*. 2016;30(6):1236–46. doi:10.1002/jcla.22009.
20. Ezzeldin E, Abo-Talib NF, Tammam MH. UPLC-Tandem Mass Spectrometry Method for Simultaneous Determination of Fluoxetine, Risperidone, and Its Active Metabolite 9-Hydroxyrisperidone in Plasma: Application to Pharmacokinetics Study in Rats. *J Anal Methods Chem*. 2017;2017:5187084. doi:10.1155/2017/5187084.
21. Zhang G, Jr AVT, Bartlett MG. Liquid chromatography/tandem mass spectrometry method for the simultaneous determination of olanzapine, risperidone, 9-hydroxyrisperidone, clozapine, haloperidol and ziprasidone in rat plasma. *Rapid Commun Mass Spect*. 2007;21(6):920–8.
22. Vasagam GA, Smith AA, Nawas CH, Kumar MS, Muthu AK, Manavalan R. 2010.
23. Kulkarni S, Chhabra G, Shivani M. Development and validation of UV spectrophotometric method for the determination of risperidone in bulk and tablets formulation. *Int J Pharm Chem Res*. 2012;1(2):1–5.
24. Kumar MS, Smith AA, Vasagam GA, Muthu AK, Manavalan R. Development of analytical method for risperidone by UV spectrophotometry. *Int J Pharm Sci Res*. 2010;1(2):122–6.
25. Siddiqui MR, Alothman ZA, Rahman N. Analytical techniques in pharmaceutical analysis: A review. *Arabian J Chem*. 2017;10(1):1409–21. doi:10.1016/j.arabjc.2013.04.016.
26. Svirskis D, Sejdic JT, Garg S. A stability indicating HPLC method for the determination of electrochemically controlled release of risperidone. *J Chromatogr Sci*. 2011;49(10):780–5. doi:10.1093/chrsci/49.10.780.
27. Dedania ZR, Dedania RR, Sheth NR, Patel JB, Patel B. Stability indicating HPLC determination of risperidone in bulk drug and pharmaceutical formulations. *Int J Anal Chem*. 2011;2011:124917. doi:10.1155/2011/124917.
28. Imam SS, Aqil M, Akhtar M, Sultana Y, Ali A. Optimization of mobile phase by 3 2-mixture design for the validation and quantification of risperidone in bulk and pharmaceutical formulations using RP-HPLC. *Anal Methods*. 2014;6(1):282–8. doi:10.1039/C3AY41562G.
29. Suthar AP, Dubey SA, Patel SR, Shah AM. Determination of Risperidone and forced degradation behavior by HPLC in tablet dosage form. *Int J Pharm Tech Res*. 2009;1(3):568–74.
30. Baldania SL, Bhatt KK, Mehta RS, Shah DA. RP-HPLC Estimation of Risperidone in Tablet Dosage Forms. *Indian J Pharma Sci*. 2008;70(4):494–7. doi:10.4103/0250-474X.44601.
31. El-Sherif ZA, El-Zeany B, El-Houssini OM. High performance liquid chromatographic and thin layer densitometric methods for the determination of risperidone in the presence of its degradation products in bulk powder and in tablets. *J Pharm Biomed Anal*. 2005;36(5):975–81. doi:10.1016/j.jpba.2004.07.014.
32. Mennickent S, Diego MD, Liser B, Trujillo L. Stability indicating HPLC method for quantification of risperidone in tablets. *J Chilean Chem Soc*. 2018;63(3):4150–4. doi:10.4067/s0717-97072018000304150.
33. Anthony GK. Development and Validation of RP-HPLC method for simultaneous estimation of Risperidone and Haloperidol in tablet dosage forms. *Int J Pharm Drug Anal*. 2014;6(6):659–61.
34. Patel RB, Patel BG, Patel MR, Bhatt KK. HPTLC method development and validation for analysis of risperidone in formulations, and in-vitro release study. *Acta Chromatographica*. 2010;22(4):549–67. doi:10.1556/AChrom.22.2010.4.5.

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