DETERMINATION OF IMPURITIES OF RISPERIDONE API BY ULTRA PERFORMANCE LIQUID CHROMATOGRAPHY (UPLC)

L.P. Magar^{1,2,*}, B. H. Zaware¹, C. J. Laheru³, Dharmendra.Singh²,
S.J. Takate¹ and M.K.Gupta²

¹Chemistry Department, New Arts, Commerce & Science College, Ahmednagar-414001,
Maharashtra, India.

²IPCA Laboratories Ltd. R &D, Kandivali Industrial Estate, Mumbai-40006, Maharashtra India.

³Chemical and Analytical Researcher, Working in Pharmaceutical Industries, Maharashtra, India

*E-mail: laki.magar@rediffmail.com

ABSTRACT

Modern research and development on medicine for various brain diseases, out of these diseases psychotic is the major problem, to overcome this problem scientist evolved medicine that is Risperidone⁵. It is an antipsychotic drug. In this study, approached a new analytical method¹ to determine the majority of impurities e.g. pharmacopeial [United state pharmacopeia]², European pharmacopeia³ and non-pharmacopeial i.e. An abbreviated new drug application [ANDA]⁴. Impurities of Risperidone analyzed by Ultra performance liquid chromatography.UPLC is advance techniques that give fast separation with a short period and have High pressure than HPLC with less consumption of solvents and buffers¹². This UPLC has many advantages for the analysis of drug products¹³⁻¹⁴ by using this concept achieved the separation of peaks of Risperidone impurities, so UPLC is very preeminent techniques for the analysis of API and drug products in pharmaceutical analysis¹⁵. The waters UPLC system¹⁸ in the present research paper giving the best separations of total fourteen risperidone impurities as per the requirement of pharmacopeia.

Keywords: Impurity Profile, Risperidone, Ultra Performance Liquid Chromatography, Related Substances, Analytical Method.

© RASAYAN. All rights reserved

INTRODUCTION

Risperidone comes in an antipsychotic drug used to treat schizophrenia schizoaffective disorder¹⁷, it is marketed throughout the globe is not only the regulatory market but also in the non-regulatory market. Determined the impurity profile of Risperidone as per different pharmacopeia. To avoid repeat testing, proposal for a single method which could possible to determine all impurities (USP, Ph.Eur, and ANDA) prescribed in an individual monograph by generated equivalency and comparison of results of batch analysis.(Pharmacopeial methods versus Proposed single method).

Classification of Impurities as per Pharmacopeia^{2,3}

E-Oxime(As per US pharmacopeia) Impurity-A (As per Ph.Eur.), Z-Oxime(As per US pharmacopeia) Impurity-B (As per Ph.Eur.), 9-Hydroxy Risperidone(As per US pharmacopeia) Impurity-C (As per Ph.Eur.), 5-Fluoro Risperidone, 6-Methyl Risperidone(As per US pharmacopeia) Impurity-D (As per Ph.Eur.), Desfluoro Risperidone(As per US pharmacopeia) Impurity-K (As per Ph.Eur.), Risperidone Difluoro ketone(As per US pharmacopeia) Impurity-H (As per Ph.Eur.), Related compound-G(As per US pharmacopeia), Impurity-F(As per Ph.Eur.), Impurity-L(As per Ph.Eur.), Impurity-M(As per Ph.Eur.), Cis N-Oxide(As per ANDA), Trans N-Oxide(As per ANDA) and Bicyclo impurity(As per ANDA).

Planned to be performed experiments by injecting all individual impurity mentioned in the individual monograph on each pharmacopeial method and we observed that, each method was capable and enough sense to detected mentioned impurities in the pharmacopeia but these methods had a limitation in terms of

Rasayan J. Chem., 13(2), 940-948(2020)

<http://dx.doi.org/10.31788/RJC.2020.1325632>

sensitivity i.e. not enough sensitive and also incapable to detect newly introduced impurities on it. Following are the limitation of pharmacopeial methods.

Limitation of Related Substances method as per European pharmacopeia³

After injecting all impurities (Ph.Eur, USP and ANDA) on related substances by HPLC method as per Ph.Eur.it revealed that, Cis-N-oxide, Bicyclo impurity and Impurity-A not adequately separated⁶ at Retention time 10.3 minute. Furthermore, Trans-N-oxide and Impurity-K not adequately separated⁶ at Retention time 14.1 minute and Impurity-H and Impurity-D not adequately separated^[6] at Retention time 15.0 minute.

Limitation of Organic Impurities Method as per United State Pharmacopeia²

After injecting all impurities (Ph.Eur, USP, and ANDA) on Organic impurities by LC as per USP, it revealed that the peak shape of Bicyclo impurity was improper⁶ and it also not adequately separated⁶ with Impurity-A as per Ph.Eur(E-Oxime impurity as per USP). In addition to that resolution⁶ in between Bicyclo impurity and Cis-N-Oxide is less than 1.5, Furthermore, Trans-N-oxide Impurity was not adequately separated⁶ with Impurity-D as per ph. Eur. at Retention time 14.64 minute.

To overcome the above limitation established new Analytical method^{1,6} which addressed each impurity of individual pharmacopeia (i.e.USP, Ph.Eur and ANDA) on a single method, further validated the same method. This article depicted in detail chromatography, critical attributes (observations) during the experiment performed within the laboratory.

Determination of impurity profile on Waters (H-Class system), gradient elution of Ammonium acetate, Acetonitrile and Tetrahydrofuran used, at wavelength 260nm with flow rate 0.3ml/minute on Waters Acquity BEH C18 ,100 mm x 2.1mm.1.7micron UPLC column at column oven temperature 72-degree centigrade.

EXPERIMENTAL

Chemicals

HPLC grade water, Acetonitrile, and tetrahydrofuran from Merck (India)⁷.Ammonium acetate from Merck(Emparta ACS)⁷.HPLC grade water from the Millipore system (Millipore Inc.USA)⁷ was used for the analysis. The samples used for the development of the Analytical method for the Impurity profile of Risperidone was received from Ipca laboratories ltd. (Ratlam site),India.⁸

Instrumentation and Chromatographic Conditions

A Waters Acquity UPLC H-Class system equipped with Acquity TUV detector was used for Analytical method development , forced degradation studies and Analytical method validation. The UPLC column Waters Acquity BEH C18 100 mm x 2.1mm 1.7micron at column oven temperature 72-degree centigrade. Weighed accurately 2.0g of Ammonium acetate on calibrated weighing balance and transferred it into the 1000 ml of HPLC grade water as a mobile phase-A, mobile phase-B as an Acetonitrile and tetrahydrofuran as a mobile phase-C in gradient elution with flow 0.3ml/min.Gradient composition was optimized as time (minute); mobile phase- A(v/v): mobile phase- B(v/v): mobile phase-C(v/v) in the ratio as T₀;90:5:5 ; T_{12.5};70:25:5, T₁₇;70:25:5, T_{17.2};90: 5:5 and T₂₅;90:5:5.The injection volume was 1 microliter. Recorded the analytical data at wavelength 260 nm by Empower software.

Preparation of Impurity Standards and Sample Preparations for the Analysis

Preliminary preparation of diluent from Mobile Phase- A and HPLC grade Methanol in the composition of (90:10) v/v. In addition to that prepared separate stock for each impurity of 100 micrograms per milliliter in a diluent which was used for specificity and further prepared 1.2 micrograms per milliliter standard solution for E-Oxime (As per US pharmacopeia) Impurity-A (As per Ph.Eur.), Z-Oxime(As per US pharmacopeia) Impurity-B (As per Ph.Eur.),9-Hydroxy Risperidone(As per US pharmacopeia) Impurity-C (As per Ph.Eur.),5-Fluoro Risperidone,6-Methyl Risperidone(As per US pharmacopeia) Impurity-D (As per Ph.Eur.), Desfluoro Risperidone(As per US pharmacopeia) Impurity-K (As per Ph.Eur.), Risperidone Difluoro ketone(As per US pharmacopeia) Impurity-H (As per Ph.Eur.), Related compound-G(As per US pharmacopeia), Impurity-F(As per Ph.Eur.), Impurity-L(As per Ph.Eur.),

Impurity-M(As per Ph.Eur.), Cis N-Oxide(As per ANDA), Trans N-Oxide(As per ANDA), Bicyclo impurity(As per ANDA) and Risperidone standard.

Separate preparation of as such a sample of Risperidone API; Prepared 1500 micrograms per milliliter in the diluent. In addition to that separately prepared of Spike solution of Risperidone by doping all above impurities into the same solution of Risperidone API which having a concentration 1500 microgram per milliliter and impurities of 1.2 micrograms per milliliter.

Analytical Procedure to Collect Systematic Data

Injected equal volume i.e.1 microliter of a single injection of Blank, six replicate injections of standard (all impurity mixture), a single injection of the sample without doped impurities and Single injection of Spiked all impurities to demonstrated the results precise, accurate and liner. % Relative standard deviation⁶ obtained from all impurity mixture should be no more than 5.0%⁶ for each impurity along with Risperidone standard.

Critical Attributes of the Analytical Method Concerning Reproducibility of Analytical Method

- To increase the Resolution⁶ in between Impurity-F and Trans-N-Oxide then decreased the Column Oven temperature from 72 Degree centigrade to 71 Degree centigrade.
- All solutions protected from Light to avoid degradation of Risperidone and its related impurities.

RESULTS AND DISCUSSION

IUPAC names of the impurities are tabulated in Table-1.

Table -1: Names and IUPAC Names of Impurities

Name of Impurity	IUPAC Name of Impurity
Impurity- B	3-[2-[4-[(Z)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyridol{1,2a}pyrimidin-4-one Z-Oxime As per USP
Impurity- A	3-[2-[4-[(E)-(2,4-difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyridol{1,2a}pyrimidin-4-one E-Oxime As per USP
Impurity- D	Risperidon 5-Fluoro Isomer; 3-[2-[4-(5-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Risperidone Ph.Eur. Impurity D
Impurity- C	9-Hydroxy Risperidone Paliperidone ; (9RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Risperidone Ph.Eur. impurity C
Impurity- F	Risperidon Carboxylate Impurity; 2-[2-Methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-3-yl]ethyl-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1- carboxylate Risperidone Ph.Eur. Impurity F
Impurity- E	6-Methyl Risperidone ; 2,6-Dimethyl Risperidone : (6RS)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Risperidone Ph.Eur. Impurity E
Related compound- G	3-{2-[4-(4-fluoro-2-hydroxybenzoyl)piperidin-1-yl]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (USP-Impurity)

Impurity –K	3-[2-[4-(1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl-2-methyl]-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Desfluoro risperidone
Impurity-L	Risperidone chloro impurity; 3-(2-chloroethyl)-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-(1,2-a)-pyrimidin-4-one Risperidone Ph.Eur. Impurity L
Impurity-M	Risperidone amine impurity (HCl Salt); paliperidone USP RC B; 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole hydrochloride Risperidone Ph.Eur. impurity M
Impurity –H	Risperidone difluoroketone; 3-[2-[4-(2,4-difluorobenzoyl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one Risperidone Ph.Eur. Impurity H
Cis N-Oxide	(1s,4r)-4-(6-fluorobenzo[d]isoxazol-3-yl)-1-(2-(2-methyl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)piperidine 1-oxide Risperidone cis-N-Oxide
Bicyclo impurity	3-(4-fluoro-2-hydroxyphenyl)-1-(2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)-1,2-diazabicyclo[2.2.2]oct-2-en-1-ium iodide Bicyclo Risperidone
Trans N- Oxide	(1s,4r)-4-(6-fluorobenzo[d]isoxazol-3-yl)-1-(2-(2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)piperidine 1-oxide Risperidone Trans N- Oxide

Specificity^{9,11}

Risperidone UPLC analytical method developed by injecting each impurity and identified the Retention time and Relative retention time of below-mentioned table and representative UPLC chromatograph depicted as a reference.

Table-2: Retention Time and Relative Retention Time

Name of Impurity	Retention Time(minute)	RRT(w.r.t.Risperidone Peak)
Impurity-A	4.605	0.566
Impurity-B	5.522	0.679
Impurity-C	6.515	0.801
Impurity-D	7.510	0.924
Impurity-E	10.569	1.300
Impurity-F	14.875	1.829
Related compound-G	8.631	1.061
Impurity-H	6.996	0.860
Impurity-K	6.182	0.760
Impurity-L	4.095	0.504
Impurity-M	2.405	0.296
Bicyclo impurity	3.184	0.392
Trans N-oxide	5.968	0.734
Cis N-Oxide	3.626	0.446
Risperidone	8.131	1.000

Evolution of Relative Response Factor^{9,11}

Response factor for each impurity evaluated by preparing exact concentration of each impurity including Risperidone standard according to limit level specification¹⁰ run the replicate injections of a mixture of the solution, refer below-mentioned table of impurity limit and specification as per Ph.Eur, USP, and ANDA.

Peak Results

	Name	RT	Area (μV*sec)	% Area	Height (μV)	USP Tailing	USP Plate Count	USP Resolution	Int Type	Manual
1	Impurity-M	2.343	1836	0.04	469	1.97	9555		BB	No
2	Bicyclo Impurity	3.173	8075	0.19	1672	1.84	11298	7.30	BB	No
3	Cis-N-oxide	3.717	6026	0.14	1300	1.53	16140	4.41	BB	No
4	Impurity-L	4.180	2684	0.07	678	1.03	20921	3.90	BB	No
5	Impurity-A	4.764	5437	0.13	1044	1.46	20255	4.54	BB	No
6	Impurity-B	5.707	7516	0.18	1353	1.30	26005	6.58	BB	No
7	Trans-N-oxide	6.147	3402	0.08	609	1.17	23294	2.97	BB	No
8	Impurity-K	6.393	3303	0.08	586	1.26	25565	1.64	BB	No
9	Impurity-C	6.712	7476	0.17	1241	1.64	23290	2.33	BB	No
10	Impurity-H	7.225	3940	0.09	571	1.89	27654	2.94	BB	No
11	Impurity-D	7.740	6284	0.15	952	1.19	32093	2.85	BB	No
12		8.080	589	0.01	95	0.94	48703	2.11	BB	No
13	Risperidone	8.420	4196340	98.19	59555	0.90	32554	2.02	BV	No
14	Related compound-G	8.859	10579	0.25	1502		32857	2.17	VB	No
15	Impurity-E	10.821	7093	0.17	976	1.21	51982	9.58	BB	No
16	Impurity-F	15.157	2871	0.07	321	1.04	67860	18.22	BB	No

Fig.-1: Representative UPLC Chromatography; Spiked^{9,11} with all Impurities in RisperidoneSpecification Limit¹⁰ Table

Table-3: Name of Impurity and Specification Limit

Name of Impurity	Specification limits
Impurity-B	NMT 0.20%
Impurity-A	NMT 0.20%
Impurity-D	NMT 0.20%
Impurity-C	NMT 0.20%
Impurity-F	NMT 0.10%
Impurity-E	NMT 0.20%
Related compound -G	NMT 0.10%

Impurity-K	NMT 0.10%
Impurity-H	NMT 0.10%
Impurity-M	NMT 0.10%
Impurity-L	NMT 0.10%
Bicyclo impurity	NMT 0.15%
Trans N-oxide	NMT 0.15%
Cis N-Oxide	NMT 0.15%
Highest unknown Impurity	NMT 0.10%
Total Impurities	NMT 0.30%

Once, injecting replicate injections of Impurities mixture and Risperidone standard obtained area response, a calculated average area further applied exact concentration and potency of individual impurities obtained response factor. Furthermore, calculated response factor each individual divided by the response factor of Risperidone. Calculated Relative response factor individual impurities tabulated as below in Table-4, which shows Relative response Factor^{9,11} for each impurity concerning Risperidone at wavelength 260 nm.

Table-4: Name of Impurity and Relative Response Factor(w.r.t.Risperidone)

Name of Impurity	Relative Response Factor(w.r.t.Risperidone)
Impurity-A	0.75
Impurity-B	0.99
Impurity-D	0.82
Impurity-C	0.95
Impurity-F	0.80
Impurity-E	0.92
Related compound-G	2.45
Impurity-K	0.88
Impurity-H	0.86
Impurity-L	1.10
Impurity-M	0.45
Bicyclo impurity	1.52
Trans N-oxide	0.59
Cis N-Oxide	0.98
Risperidone	1.00

Established (% w/w) Recovery(Accuracy)^{9,11} Data

To established accuracy data, we prepared each impurity doped into the Risperidone solution from LOQ level to 150 concerning specification limits and obtained below-mentioned results by injecting triplicate injections of each level. The representative Chromatograph for Recovery Study shown in below-mentioned Chromatographs (Fig.-2 and 3).

Table-5: Name of Impurity and Average (% w/w) Accuracy From Triplicate Injection

Name of Impurity	Average (% w/w) Accuracy From Triplicate Injection			
	LOQ Level w.r.t. Specification Limit	80% Level w.r.t. Specification Limit	100% Level w.r.t. Specification Limit	150%level w.r.t. Specification Limit
Impurity-A	97.51	101.01	99.61	101.10
Impurity-B	106.58	100.51	99.90	99.48
Impurity-C	102.35	101.69	99.48	101.43
Impurity-D	107.26	106.15	104.31	104.94
Impurity-E	103.77	104.26	106.03	104.34

Impurity-F	96.72	101.19	95.67	96.40
Related compound-G	61.56*	81.76	82.96	90.24
Impurity-H	113.50	110.56	106.53	105.23
Impurity-K	136.06	115.25	113.34	113.47
Impurity-L	105.98	107.53	106.51	105.84
Impurity-M	95.37	97.35	90.46	95.25
Bicyclo impurity	108.40	107.80	104.17	103.82
Trans N-oxide	103.06	103.08	102.07	102.35
Cis N-Oxide	114.54	108.25	100.33	95.56

*Related compound-G eluted closely to the Risperidone peak to improve resolution in between this two peak washed the UPLC column with following procedure i.e initially wash the UPLC column with water: Acetonitrile(80:20)v/v for 30 minutes and then Water: Acetonitrile(20:80)v/v for 30 minutes then initiate the analysis.

Fig. -2 Sample (without Doping impurities-Risperidone API)

Fig.-3 Spiked Sample (Doping Impurities with Risperidone API)

Established Precision Data^{9,11}

To establish precision data, we prepared each impurity doped into the Risperidone solution 100% level six different preparations of spike sample concerning specification limits and injected single injection and established precision data tabulated as below (Table-6).

Table-6: Name of Impurity and (% w/w) Recovery

Name of Impurity	(% w/w) Recovery					
	Spike prep-1	Spike prep-2	Spike prep-3	Spike prep-4	Spike prep-5	Spike prep-6
Impurity-A	99.61	100.86	100.19	99.78	103.93	101.98
Impurity-B	99.58	101.17	99.90	101.69	99.22	99.70

Impurity-C	99.88	99.48	101.29	99.96	99.00	100.18
Impurity-D	104.40	104.31	104.14	103.03	103.92	104.71
Impurity-E	105.13	103.52	104.37	106.99	104.52	105.21
Impurity-F	99.02	97.97	95.67	92.15	98.79	100.02
Related Compound-G	82.96	83.61	85.33	83.69	85.52	83.59
Impurity-H	106.53	106.15	102.82	103.51	106.68	105.05
Impurity-K	114.09	113.24	113.16	114.04	118.52	118.61
Impurity-L	106.51	105.25	107.06	109.17	106.25	105.72
Impurity-M	85.85	90.46	93.16	97.96	96.60	99.72
Bicyclo impurity	102.54	104.17	103.47	104.23	105.54	105.39
Trans N-oxide	101.53	102.07	105.29	102.73	104.83	103.86
Cis N-Oxide	100.33	101.27	102.52	95.58	86.98	80.85

Established Linearity Data^{9,11}

Linearity data fetched from Accuracy, we prepared each impurity doped into the Risperidone solution. LOQ level to 150% level single preparation of spike sample concerning specification limits and injected triplicate injection and established linearity data tabulated as below (Table-7).

Table-7: Name of Impurity and Average Area Response From Triplicate Injection after Spiking

Name of Impurity	Average Area response from Triplicate Injection after Spiking				R ² Value
	LOQ Level w.r.t. Specification Limit	80% Level w.r.t. Specification Limit	100% Level w.r.t. Specification Limit	150% level w.r.t. Specification Limit	
Impurity-A	1544	4253	5266	8096	0.9993
Impurity-B	1813	5883	7299	11212	0.9996
Impurity-C	2533	6033	7502	11357	0.9992
Impurity-D	2669	5068	6280	9484	0.9932
Impurity-E	2485	5683	7301	10731	0.9988
Impurity-F	1521	3336	4183	6110	0.9994
Related compound-G	1680	6003	7854	12420	0.9997
Impurity-H	1631	3069	3762	5551	0.996
Impurity-K	1348	3072	3822	5475	0.9996
Impurity-L	1210	3291	4183	6110	0.9993
Impurity-M	589	1173	1597	2351	0.9906
Bicyclo impurity	1831	6808	8209	12331	0.9957
Trans N-oxide	1041	2788	3554	5318	0.9998
Cis N-Oxide	1266	4406	5219	7647	0.9924

CONCLUSION

This work of risperidone impurities separation by UPLC instrument than other research papers¹⁶ is novel. From the above analytical method development, analytical method validation data and interpretation, it is observed that this analytical method is well specified and adequately separated from each impurity. In addition to this, this method is accurate, precise, linear concerning each specified impurity, and also enough sensitive to detect all known and unknown impurities as well as principle uses and application of UPLC is very high for the reduction of cost with time in the pharmaceutical company¹⁹. UPLC can be used with multidetector for the analysis of API, impurities and drug products. Therefore, it has high advantages as well as application.²⁰

ACKNOWLEDGMENT

This research publication is a globally intended purpose for a human being. Furthermore, we (authors) of this publication thankful and congratulate all members of R & D Ipca Laboratories Ltd., who are participating in the process of Analytical research and development activities like Analytical method development, validation, etc.

REFERENCES

1. R. Snyder, J. Kirkland, L. Glajch. Practical HPLC Method Development, Second Edition, pp28-29, (1997), DOI:10.1002/9781118592014
2. <https://www.usp.org/compounding/bulk-drug-substances-monographs>
3. <https://www.edqm.eu/en/knowledge-database>
4. <https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda>
5. <https://en.wikipedia.org/wiki/Risperidone>
6. <https://www.gmp-compliance.org/gmp-news/new-usp-draft-for-general-chapter-621-chromatography-with-impact-on-hplc-system-suitability-tests>
7. http://www.merckmillipore.com/IN/en/products/reagents-chemicals/labware/jEyB.qB.xZ4AAAE_X_x3.Lxi,nav
8. <https://www.ipca.com/active-pharmaceutical-ingredient-products.html>
9. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-2-r1-validation-analytical-procedures-text-methodology-step-5_en.pdf
10. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-6-test-procedures-acceptance-criteria-new-drug-substances-new-drug-products-chemical_en.pdf
11. https://database.ich.org/sites/default/files/Q2R2-Q14_EWG_Concept_Paper.pdf
12. M. Taleuzzaman, S. J. Ali, Gilani, S. S. Imam, A. Hafeez, *Austin Journal of Analytical and Pharmaceutical Chemistry*, **2(6)**, 1056 (2015)
13. A. D. Jerkovich, J. S. Mellors, J. W. Jorgenson, *LCGC*, **21**, 606 (2003)
14. M. E. Swartz, B. Murphy, *Lab Plus International*, 18 (2004)
15. M. E. Swartz and B. Murphy, *Pharmaceutical Formulation Quality*, 40 (2004)
16. T. Nejedly, P. Pilarova, P. Kastner, Z. Blazkova, *International Journal of Research in Pharmacy and Chemistry*, **4(2)**, 261 (2014)
17. <https://www.fitzgerald-fii.com/risperidone-impurity-50r-r68808.html>
18. https://www.waters.com/waters/en_US/UPLC---Ultra-Performance-Liquid0%20%20Chromatography-Beginner%27s-Guide/nav.htm?cid=134803622&locale=en_US
19. G. Chawla, C. Ranjan, *Open Chemistry Journal*, 1-16 (2016), DOI:10.2174/1874842201603010001 [RJC-5632/2019]