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DETERMINATION OF RISPERIDONE IN PHARMACEUTICAL PRODUCTS BY UV-SPECTROPHOTOMETRY AND RP-HPLC: METHOD DEVELOPMENT AND VALIDATION

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ABSTRACT

The present work describes a simple, reproducible, economical and rapid analytical method for the determination of Risperidone and its application in commercially available dosage form. In this respect RP-HPLC and UV/Visible Spectrophotometric methods were developed and validated for estimation of Risperidone in Pharmaceutical Formulations. In HPLC method the separation of analyte was carried by using Octadecylsilane Column C_{18} (4.6mm x15 cm) and mobile phase having fixed composition of Water and Acetonitrile in the ratio of 65:35 v/v was used at pH 3.0 and at a flow rate of 1.0 ml/min. Detection was carried out at 275 nm. Retention time for Risperidone was found to be 5.097 min, while in spectrophotometric method the λ max of the Risperidone was determined by performingrepetitive scans of Risperidone sample solutions in the entire UV region. Only one peak was observed in all scans at wavelength of 237 nm.Standard and Sample solutions were made in 0.2 N HCl. In both the HPLC and UV/Vis. spectrophotometric methods, the mean content of Risperidone in the five different brands of tablets were within the USP limit i.e. 95%-110%. Thus it was proved that the proposed HPLC method can be successfully used for the commercially available resperidone brands. The developed methods were validated in accordance with the current International Conference on Harmonization guidelines and

validated against certain parameters like Accuracy, Precision, Specificity, Linearity, Robustness, Limit of Detection (LOD) and Limit of Quantitation (LOQ).

Keywords: Risperidone, RP-HPLC, Validation, UV/Visible, USP

INTRODUCTION

Risperidone is an atypical antipsychotic agent belonging to the chemical class of Benzisoxazole derivatives for the acute and long term treatment of Schizophrenic patients. Risperidone action is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2($5HT_2$) receptor antagonism. It is the potent antagonist of both dopamine and serotonin receptors [1-4].

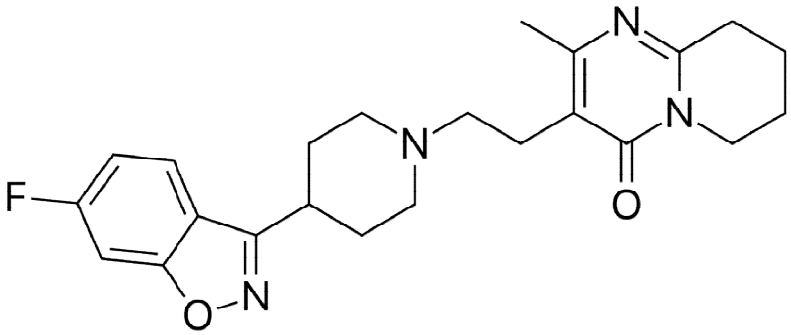

Figure 1: Chemical structure of Risperidone

It is administered orally and completely metabolized. Less than 1% is excreted unchanged percent is excreted unchanged and moreover Risperidone plasma protein binding is 90 %.9-hydroxyrisperidone is the main principal metabolite of Risperidone [3, 5, 6]. Pharmacokinetics of Risperidone and 9-hydroxyrisperidone is linear, when given in the dosing range of 12.5 mg to 50mg, whereas there is slight initial release of a drug when given Intra muscular i.e.< 1 % of the dose [7, 8]. After given intramuscular the drugreleases start from three weeks onward, which will maintained from four to six weeks [9-12]. The volume of distribution is one 2L/kg [13]. Risperidone is mostly metabolized where as the result of metabolism of Risperidone which is done through hydroxylation of Risperidone to 9- hydroxyrisperidone by the CYP2D6 enzyme [14, 15].

Pharmaceutical Analytical Chemistry is an important part in monitoring the quality of pharmaceutical products for safety and efficacy [15-17]. With the advancement in the development of new synthetic compounds and drugs, the scope of Pharmaceutical Chemistry has enhanced to higher levels [1, 18-20]. With the increase demand of neuroleptic drugs throughout the world, there is a need to develop simple, rapid and less expensive analytical testing methods.This research work aims to develop anactive contribution in literature

by developing simple, rapid and cost effective analytical testing method of Risperidone.

MATERIAL AND METHODS

Instrumentation and analytical techniques

An isocratic HPLC – 20A Shimadzu system consisted of HPLC Pump- Perkin Elmer 200LC with online degasser, Rheodyne manual injector having loop and Column C18 (L1 Packing 5µm, 4.6x 15 cm), pH Meter (Orion 3) was used, Sonicator (Elmasonic E60 H), Vortex Mixer (Seouline Bio Scirnce-Korea), Membrane filters i.e. 0.45µm (Sartorius, Germany), micropipette (Softpet – Finland), Filtration assembly (Pyrex, France), Weighing balance (Shiadzu AUW220) and distillation plant (WDA/4 R & M England). HPLC system was operated at ambient temperature using a flow rate 1ml/min. UV-detector was set 270nm.

Materials

Risperidone was received as generous gift Schazoo Zaka Pharmaceutical's Lahore. Acetonitrile, Hydrochloric acid and Trifluro-acetic acid of HPLC grade were purchased from Merck, Germany. Distilled water was freshly prepared in the Pharmaceutics research lab. All the chemicals used were of analytical grade.

Preparation of Mobile phase

Mobile phase was consists of water (65%) and acetonitrile (35%), these solvents were accurately measured using volumetric flask and mixed properly by vortexing. pH of the mobile phase was adjusted to pH 3.0 by trifluroacetic acid and filtered through membrane filter using filtration assembly. Mobile phase was also prepared in other proportions too i.e. (35:65), (50:50), (25:75) and (75:25) but the most suitable mobile phase was 65:35 in terms of peak shape and retention time. Retention time was increased with the rise of water content of the mobile phase and by decreasing its pH. Retention time observed by injecting 20µl of the sample was near 5.097min as shown in Figure 2.

Stock and working solutions

Different amounts of Risperidone were consumed to prepare stock as well as dilutions. 52.7mg, 26.35mg, 13.17mg, 6.587mg and 3.29mg were dissolved separately in 100ml mobile phase to prepare respective stock solutions. 2mL of each solution was taken in 50mL flask and diluted with mobile phase to yield desired dilutions i.e. 0.021mg/ml, 0.0105mg/ml, 0.0052mg/ml, 0.0026mg/ml and 0.0013mg/ml. These solutions were used to develop standard curve from area under the curve obtained at 270nm.

Method validation

Specificity

It is the ability of a method to measure the response of a particular compound in the

presence of its degradation contents or other substances. Specificity of a particular compound should remain same even in the presence of excipients and RSD values should be in 2% limits. Five injections of standard while three injections of the sample were injected each time into the chromatographic system and retention times were noted.

Linearity

Six non-zero concentrations were selected i.e. 0.021, 0.024, 0.027, 0.03, 0.033, 0.036 mg/ml. Five injections of each concentration were injected into the HPLC system and their peak areas were recorded at wavelength 270nm. Calibration curve was plotted between these concentrations as well as their respective peak areas. Straight line equation i.e. y = ax + b was fitted using Microsoft excel and value of regression co-efficient was calculated that was 0.998 in this case. %RSD should be less than 2%.

Accuracy

Three known concentrations i.e. 0.021mg/ml, 0.031mg/ml and 0.036mg/ml of the sample as well as standard were injected in triplicate to the chromatographic system and their peak areas were calculated. % recoveries of the Risperidone from samples and standard were also compared. For acceptance criteria %RSD values must be lower than 2%.

Precision

Precision (both Intra-day and Inter-day for 3 days) studies were performed at 70% (0.021mg/ml), 100% (0.031mg/ml) and 120% (0.036mg/ml).Three replicates of each concentration were performed. Intermediate precision was studied by running the whole method on three different days and different analyst. Each day fresh mobile phase and reagents were prepared.

Robustness

Robustness of the method was determined by analyzing standard solution under normal operating conditions and deliberate changes have been made i.e. mobile phase, pH, change in flow rate, change of column to check their effect on Risperidone retention time and peak area etc.

Lower limit of detection (LLOD) and quantification (LLOQ)

Lowest amount of an analyte that can be detected in a sample but isnot quantified. While the quantification limit is, the lowest amount of an analyte that can be quantitatively determined with adequate precision and accuracy.Five solutions of both standard and sample were prepared towards the lower concentration to find out LLOD and LLOQ (0.007, 0.0035, 0.0017, 0.0008, 0.0004 mg/ml).

RESULT AND DISCUSSION

Specificity and Retention Time

Specificity was documented by comparing the retention times obtained in the Standard preparation (3 samples) with those obtained from the product sample (3 samples).Usually, a difference with in ± 3% is considered acceptable between retention times.(Specificity results are reported in Table 1). Retention time was observed at 5.097 min shown in Figure 1. All the results of specificity by injecting three replicate injections of standard and Sample are within limits.

Linearity

In two series of six standard measuring flasks varying amount of standard stock solution of Risperidone was taken and made up to various concentrations of 0.021, 0.024, 0.027, 0.03, 0.033; 0.036 mg/ml (70, 80, 90,100, 110 and 120%) was injected from each flask. The peak area response was recorded at 270nm. Linear regression data for the calibration curve indicate that the response was linear over the concentration range of 0.021-0.036 mg/ml of standard preparation with correlation coefficient r^2 =0.998, whereas % RSD were below than 2% (*Fig. 3*).

Accuracy

Accuracy studies were performed at 70%, 100% and 120%.Three replicate of each concentration were performed. Whereas mean percentage recoveries of Risperidone was 100.01% and percentage of Relative Standard Deviation was below 2%.Hence there is no significant difference between theoretical and actual and the proposed method is shown to be accurate and selective. Data of accuracy studies are shown in Table2.All the results of relative standard deviation (RSD) by injecting three replicate injections of Risperidone standard, three replicate injection of Risperidone 2 mg tablets of three concentrations were injected are within specified limits.

The Precision (both Intra-day and Inter-day 3 days) studies were performed at 70%, 100% and 120%.Three replicate of each concentration were performed .The intermediate precision was studied by running the whole method on three different days and different analyst. Each day fresh mobile phase and reagents were prepared. The % RSD values of Intra-day Precision were < 0.065% and < 0.035% for standard and sample preparations respectively. % RSD values of Inter-day Precision (1^{st}, 2nd, 3rd day) were < 0.065, <0.069, <0.136 and<0.035 %,< 0.063, <0.267 for standard and sample preparation respectively. Mean percentage recoveries were within the limits (The data of Precision studies are shown in Table 3-6). All the results of relative standard deviation

(RSD) by injecting three (3) replicate injections of Risperidone standard, three replicate injection of Risperidone 2 mg tablets of three concentrations were injected on three consecutive days are within specified limits.

Robustness

The Robustness of the method was determined by analyzing standard solution at normal operating conditions and deliberate changes have been made like change in mobile phase, pH, change in flow rate, change of column. The % RSD values were within the limits (The data of different parameters of Robustness are shown in Table 7).Change in flow rate (1.25 ml, 1.75 ml per minute), change of Mobile phase pH (2.8, 3.2) and Change of column (C 18-25) are used. All the results of Assay %age and % RSD are well within limits.

LOD and LOQ

In Limit of Detection (LOD) and Limit of Quantitation (LOQ) study, concentrations were prepared towards the lower side of linearity/ range study. LOD will be acceptable to that concentration at which results can be easily detected. A signal- to-noise ratio between 3 or 2:1 is generally acceptable for estimating the detection limits and signal- to- noise ratio between 10:1 is generally acceptable for estimating the quantitation limit.

Five solutions of both standard and sample were prepared towards the lower concentration to find out LOD and LOQ (0.021, 0.0105, 0.0052, 0.0026, 0.0013 mg/ml). Solutions with concentration 0.021 to 0.0013 mg/ml were prepared and results were obtained. At the concentration 0.0026 mg/ml, signal-to- noise ratio was 3:1and Risperidone was easily detectable at this concentration, so it was taken as Detection limit, whereas at concentration 0.0013 mg/ml, signal-to- noise ratio was 10:1 where Risperidone was easily detectable at this concentration, therefore it was taken as Quantitation limit (The data of LOD and LOQ studies are shown in Table 8 and 9).

Assay of Different Brands of Tablets by HPLC and UV-Spectrophotometry

According to the USP-32 Monograph for Risperidone tablet, it should contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Risperidone. According to HPLC and UV-spectrophotometric method of assay, the mean content of Risperidone in the five different brands of tablets were within the USP official limit i-e 95%-110% (Fig. 4, 5).This shows that, the proposed HPLC and UV-spectrophotometric method can be successfully used for the commercially available products.

Table 1: Repetate of Risperidone preparations for Specificity

Relative Standard Deviation (RSD) of Standard triplicate injections not more than 2%					
No. of Injections	**Peak Area**	**Average**	**Retention Time**	**STDEV**	**%RSD**
1	**548769**	**553497**	**5.086**	**3371.211**	**0.609**
2	**553158**		**5.092**		
3	**557529**		**5.001**		
Relative Standard Deviation (RSD) of Sample (Tablet) triplicate injections not more than 2%					
No. of Injections	**Peak Area**	**Average**	**Retention Time**	**STDEV**	**%RSD**
1	**553403**	**552789**	**5.066**	**2441.054**	**0.441**
2	**550100**		**5.083**		
3	**554865**		**5.097**		

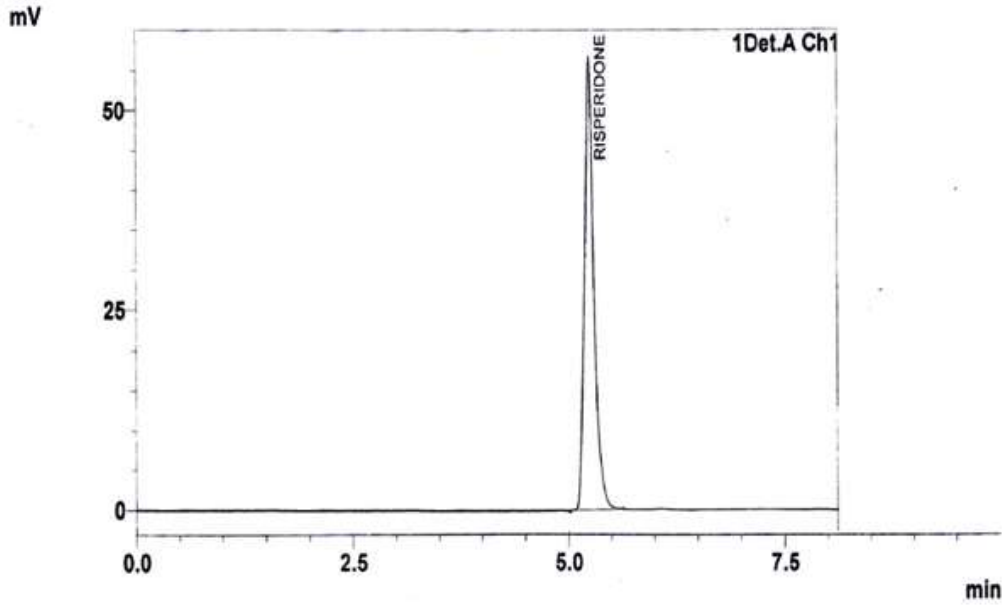

Figure 2: Risperidone chromatograph from sample in mobile phase

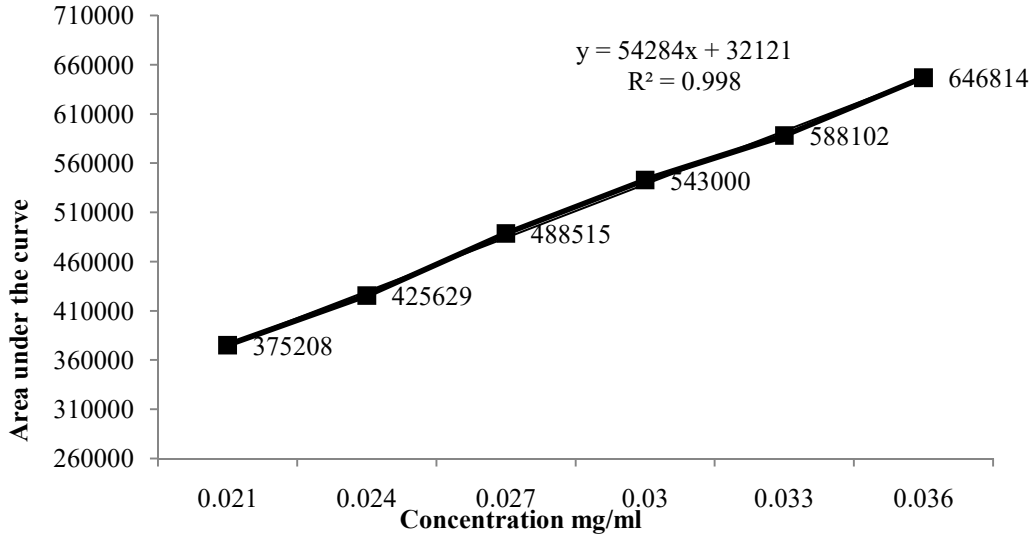

Figure 3: Standard calibration curve of Risperidone

Table 2: Repetate of standards Risperidone and tablets preparations for accuracy

Accuracy Evaluation for Standard Risperidone				
Dilutions	**No. of injections**	**Peak Area**	**STDEV**	**%RSD**
0.021 mg /ml	1	248112	224.167	0.09
	2	247664		
	3	247903		
0.03 mg / ml	1	357481	66.46	0.018
	2	357522		
	3	357611		
0.036 mg / ml	1	425704	372.214	0.087
	2	426312		
	3	426380		
Accuracy Evaluation for Risperidone Tablet				
Dilutions	**No. of injections**	**Peak Area**	**STDEV**	**%RSD**
0.021 mg /ml	1	248328	51.013	0.02
	2	248227		
	3	248290		
0.03 mg / ml	1	357486	203.593	0.056
	2	357247		
	3	357081		
0.036 mg / ml	1	425868	124.181	0.029
	2	425969		
	3	426115		

Table 3: Repetate of Risperidone standard preparation and tablets for intraday precision

For Standard Risperidone						
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**RSD %**	**Mean RSD value %**	**Limits RSD value %**
Risperidone Standard	0.021	3	247893	0.090429	0.0654	Not more than 2
	0.03	3	357538	0.018588		
	0.036	3	426132	0.087347		
For Risperidone Tablet						
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**Mean Recovery mg/ ml**	**Mean Recovery %**	**RSD %**
Risperidone 2 mg tablets	0.021	3	24828	0.021	100.156	0.020
	0.03	3	357271	0.029	99.925	0.056
	0.036	3	425984	0.035	99.965	0.029

Table 4: Repetate of Risperidone standard preparation and tablets for inter day precision (Day1st)

For standard Risperidone						
Compound	**Concentration mg/ ml**	**N**	**Average Area**	**RSD %**	**Mean RSD value %**	**Limits RSD value %**
Risperidone Standard	0.021	3	237893	0.081	0.058	Not more than 2
	0.03	3	347538	0.016		
	0.036	3	406132	0.077		
For Risperidone Tablet						
Compound	**Concentration mg/ ml**	**N**	**Average Area**	**Mean Recovery mg/ ml**	**Mean Recovery %**	**RSD %**
Risperidone 2 mg tablets	0.021	3	22656	0.020	99.134	0.019
	0.03	3	327535	0.028	99.343	0.056
	0.036	3	415463	0.034	99.775	0.028

Table 5: Repetate of Risperidone standard preparation and tablets for inter day precision (Day2nd)

			For Standard Risperidone			
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**RSD %**	**Mean RSD value %**	**Limits RSD value %**
Risperidone Standard	**0.021**	**3**	**250229.66**	**0.145186**	**0.0699**	**Not more than 2**
	0.03	**3**	**356359.11**	**0.176321**		
	0.036	**3**	**425100.33**	**0.201649**		
For Risperidone Tablet						
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**Mean Recovery mg/ ml**	**Mean Recovery %**	**RSD %**
Risperidone2mg tablets	**0.021**	**3**	**250041**	**0.0284**	**99.925**	**0.069**
	0.03	**3**	**355905**	**0.0408**	**99.872**	**0.066**
	0.036	**3**	**425737**	**0.0513**	**99.732**	**0.056**

Table 6: Repetate of Risperidone standard preparation and tablets for inter day precision (3rd day)

For Standard Risperidone						
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**RSD %**	**Mean RSD value %**	**Limits RSD value %**
Risperidone Standard	**0.021**	**3**	**249366**	**0.520**	**0.136**	**Not more than 2**
	0.03	**3**	**355886**	**0.047**		
	0.036	**3**	**429794**	**0.196**		
	For Risperidone Tablet					
Compound	**Concentration mg/ ml**	**n**	**Average Area**	**Mean Recovery mg/ ml**	**Mean Recovery %**	**RSD %**
Risperidone2mg tablets	**0.021**	**3**	**248942**	**0.0284**	**99.082**	**0.440**
	0.03	**3**	**356351**	**0.0407**	**100.130**	**0.276**
	0.036	**3**	**428437**	**0.0621**	**102.023**	**0.086**

Table 7: Repetate of Risperidone preparations for Robustness

No. of Injections	**Peak Area**		**Average Assay %**	**STDEV**		**%RSD**	
	Std. Peak	**Tablet Peak**	**95-110%**	**Std. STDEV**	**Tablet STDEV**	**Std.% RSD**	**Tablet % RSD**
Flow Rate : 1.25							
1	**660287**	**655436**	**99.26**	**4278.263**	**2755.550**	**0.652**	**0.420**
2	**652592**	**652908**	**100.04**				
3	**653199**	**658413**	**100.79**				
Flow Rate : 1.75							
1	**437764**	**437075**	**99.84**	**2648.036**	**5667.790**	**0.608**	**1.279**
2	**432500**	**443581**	**102.56**				
3	**435636**	**448367**	**102.92**				
Change of Mobile Phase pH : 2.8							
1	**582078**	**575397**	**98.85**	**3533.412**	**6025.963**	**0.609**	**1.039**
2	**577081**	**583919**	**101.18**				
Change of Mobile Phase pH : 3.2							
1	**502449**	**497615**	**99.03**	**395.272**	**4495.077**	**0.078**	**0.897**
2	**501890**	**503972**	**100.41**				
	Change of Column(18-25)						
1	**511930**	**502005**	**98.06**	**3865.045**	**1516.036**	**0.759**	**0.302**
2	**506464**	**499861**	**98.69**				

Table 8: Results for Limit of Detection

Parameter: (LOD)				Concentration: 0.0026mg/ml	
Name of API	Standard Average Area	Sample Average Area	Average %age of Samples	Signal- to- Noise Ratio	Acceptance Criteria
Risperidone	2162.5	2142.4	99.07%	1:3.2 1:3.1 1.3.3	LOD will be acceptable to that concentration at which results can be easily detected. A signal-to- noise ratio between 3 or 2:1 is generally acceptable for estimating the detection limit.

Table 9*:* Results for Limit of Quantitation

Parameter: (LOQ)				Concentration: 0.0013 mg/ml
Name of API	Standard Average Area	Sample Average Peak Area	Average %age of Samples	Signal- to- Noise Ratio 1:9.8 1:10.02 1:10.3 1:10.1 1:10.01
Risperidone	8205.2	8266.3	100.7%	

All the results of LOD& LOQ by injecting replicate injections of standard and sample respectively are within limits.

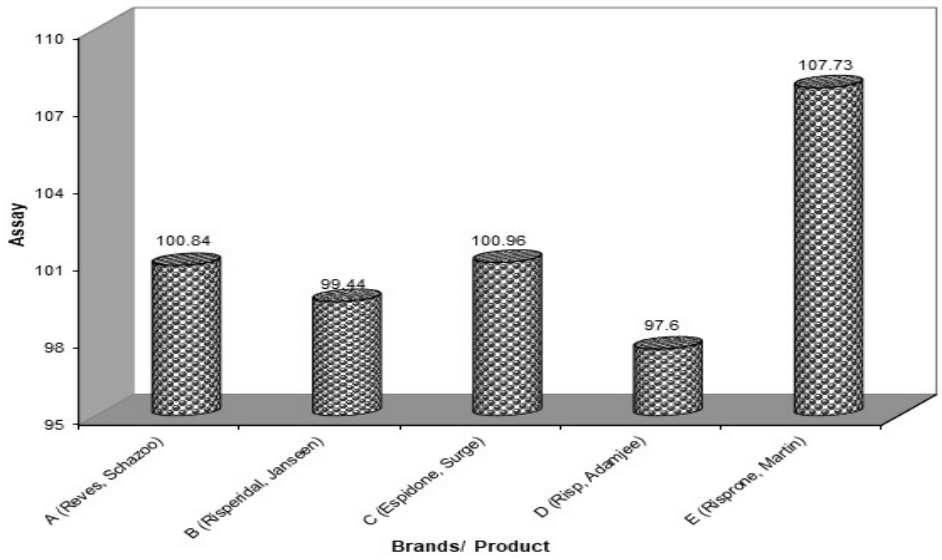

Figure 4: Average assay percent of different brands of Risperidone 2mg tablet by HPLC method

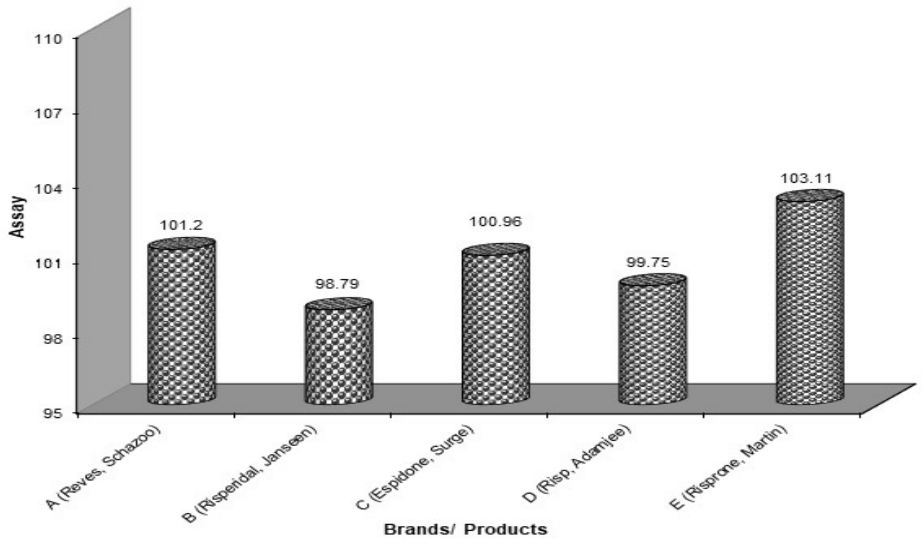

Figure 5: Average assay percent of different brands of Risperidone 2mg tablet by UV method

CONCLUSION

In the present study an attempt has been made to develop RP-HPLC and UV Spectrophotometric method for the determination of Risperidone in commercially available brands of tablet. The proposed HPLC and UV methods proved to be suitable for the analysis of Risperidone in solid dosage form. By comparing the said methods, the direct spectrophotometric determination is widely used in laborites and pharmaceutical industries and is cheaper than HPLC, but most of the Spectrophotometric methods reported suffer from disadvantages like narrow range of determination, requires heating or extraction, long time for the reaction to complete, use of non-aqueous system, stability of the colored product formed etc. HPLC exhibits more precise and accurate results, when used for the estimation of Risperidone in both pharmaceutical dosage form and sample taken from plasma and urine. Therefore HPLC is the best suited technique for the routine estimation of Risperidone in both pharmaceutical dosage form and sample taken from plasma and urine. Five different brands of Risperidone tablets were analyzed for comparative studies. All the brands of tablets contained the labeled amount of Risperidone, which revealed that the said brands was under the specified limits and delivered the same qualitative or quantitative active ingredient as promised.

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