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Design and Validation of a Stability-Indicating RP-HPLC Method for Quantifying Silodosin and Dutasteride in Both Bulk and Dosage Forms, as Well as in Human Plasma.

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KEYWORDS
RP-HPLC, Silodosin, Dutasteride, stability indicating, validation, ICH guidelines.

ABSTRACT:
A cost-effective, stability-indicating RP-HPLC method was successfully developed and validated for the simultaneous determination of Silodosin and Dutasteride in both bulk and pharmaceutical formulations. The RP-HPLC analysis utilized a C18 Column (4.6 x 250 mm, 5µm particle size), with a mobile phase consisting of mixed buffer and methanol in a 0.1% OPA in water ratio (70:30). The column temperature was maintained at 25oC, with a flow rate of 0.7 ml/min and an injection volume of 20µl. Detection was performed at 231nm. Validation of the method demonstrated linearity for Silodosin and Dutasteride in the concentration ranges of 20-100 µg/ml and 1.5-6.25 µg/ml, respectively, with regression values of 0.9997 for Silodosin and 0.999 for Dutasteride. Susceptibility studies revealed that Silodosin and Dutasteride were highly vulnerable to peroxide (19.12 & 19.50) and basic conditions (18.01 & 17.45), while exhibiting lower susceptibility to acidic (13.86 & 15.44) and hydrolytic conditions (1.11 & 0.47). Precision studies demonstrated % RSD values less than 2% for both drugs across all selected concentrations. The limit of detection (LOD) and limit of quantification (LOQ) were determined as 0.505 µg/ml and 1.53 µg/ml for Silodosin, and 0.079 µg/ml and 0.241µg/ml for Dutasteride, respectively. The method adhered to International Conference on Harmonization (ICH) guidelines during validation.

INTRODUCTION:

The development and validation of High Performance Liquid Chromatography (HPLC) methods are pivotal in various aspects of pharmaceutical drug development, discovery, and manufacturing, as well as in studies related to humans and animals. These analytical procedures are designed to examine specific characteristics of drug substances or products, comparing them against predetermined acceptance criteria. High Performance Liquid Chromatography (HPLC) emerges as the method of choice for assessing peak purity in new chemical entities, monitoring changes in reactions during synthetic procedures or scale-up processes, assessing new formulations, and conducting quality assurance for the final drug products [1-5]. HPLC has proven to be a highly effective technique that can separate, identify, and quantify compounds present in any sample that is soluble in a liquid. Widely recognized as one of the most powerful tools in analytical chemistry, HPLC significantly contributes to the comprehensive understanding and quality control of pharmaceutical compounds [16-18].

Silodosin is a chemical compound with the molecular formula (-)-1-(3-hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide. This medication is primarily prescribed for the symptomatic relief of benign prostatic hyperplasia (BPH), a non-cancerous enlargement of the prostate gland in men. Classified as an alpha-1 adrenergic receptor antagonist, Silodosin

Journal of Chemical Health Risks
www.jchr.org
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exerts its therapeutic effect by selectively targeting and blocking alpha-1 receptors in specific anatomical locations, including the prostate, bladder neck, and urethra [21].

Dutasteride, chemically known as N-[2,5-bis(trifluoromethyl)phenyl]-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide, is another medication employed primarily for the treatment of benign prostatic hyperplasia (BPH). Unlike Silodosin, Dutasteride is not only utilized for BPH associated with prostate enlargement but also finds application in addressing scalp hair loss in men. Additionally, Dutasteride is incorporated as part of hormone therapy in transgender women. The mechanism of action of Dutasteride involves the inhibition of 5-alpha-reductase, an enzyme responsible for the conversion of testosterone to dihydrotestosterone (DHT). By hindering this conversion, Dutasteride reduces the levels of DHT, a hormone implicated in the development and progression of BPH and androgenetic alopecia (male-pattern baldness) [21].

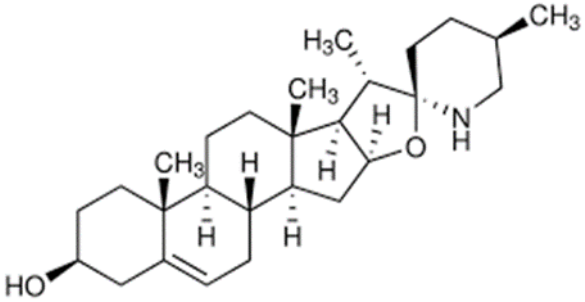

Figure 1: Structure of Silodosin

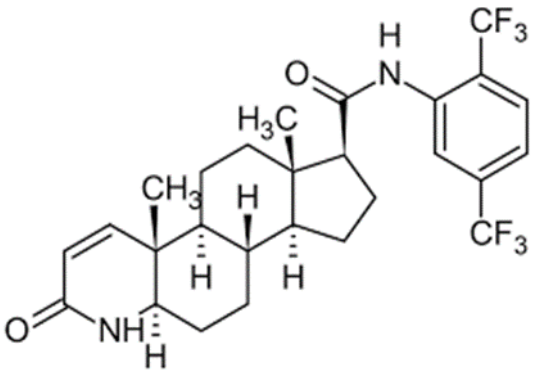

Figure 2: Structure of Deutasterid

Materials and Methods:

Chemicals and Reagents:

Silodosin and Dutasteride, essential pharmaceutical compounds, are sourced from Kopran Ltd. Ortho-Phosphoric acid, a crucial component in the analytical processes, is acquired from Avantor Performance Materials India Ltd., situated in Thane, Maharashtra. The high-quality Methanol used in these processes is obtained from Merck Specialities Pvt. Ltd., located in Shiv Sager Estate 'A' Worli, Mumbai, Maharashtra. Silodosin and Dutasteride, after meticulous extraction and synthesis, are formulated into a market-ready medication. The marketed formulation, available at local medical stores under the brand name "Rapilif D," contains Silodosin at a concentration of 4 mg and Dutasteride at 0.5 mg.

Instrumentation:

For the analytical purposes of this study, an HPLC system equipped with advanced Agilent technology was employed. This high-performance liquid chromatography (HPLC) system featured a gradient system and a UV detector for precise and effective analysis. The chromatographic separation was carried out using an Agilent C18 Column with dimensions of 4.6mm x 250 mm and a particle size of 5 µm, ensuring optimal resolution and separation of the target compounds.The HPLC instrument comprised a 940D pump, a 20µl injection loop for sample introduction, and a UV 740D Absorbance detector for sensitive detection of analytes. The entire analytical process was controlled and monitored using the Chemstation software, providing a comprehensive platform for data acquisition, analysis, and instrument control.

Preparation of the Standard Stock Solution:

A precisely measured quantity of 40 mg of Silodosin and 2.5 mg of Dutasteride was accurately weighed. The standard amount was meticulously combined with 10 ml of methanol, creating a homogeneous mixture. Subsequently, this standard mixture was added to 2 ml of untreated human plasma. The resulting solution underwent a thorough mixing through vertical shaking for a duration of 30 minutes to ensure complete homogenization of the components. Following the mixing step, the solution was subjected to centrifugation

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JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

at 5000 rpm for a duration of 1 hour. This centrifugation process facilitated the separation of solid particles or any precipitates from the liquid phase. The supernatant obtained after centrifugation was then subjected to filtration using membrane filters. This filtration step aimed to obtain a clear and particulate-free organic solution, ensuring the removal of any impurities or unwanted substances. The clarified organic solution, now devoid of particulates, was transferred into sample vials specifically designed for High-Performance Liquid Chromatography (HPLC). These sample vials were then loaded onto the HPLC system for the chromatographic run. The HPLC analysis, conducted in the subsequent steps [4-7], involved the separation and quantification of Silodosin and Dutasteride based on their distinct chromatographic characteristics.

Preparation of the Solution for Assay:

In the analysis of the marketed product, which is indicated to contain 4 mg of Silodosin and 0.5 mg of Dutasteride according to label claim, a sample was prepared by mixing it with 10 ml of methanol (MeOH). To facilitate thorough extraction, the mixture underwent a 15-minute sonication process. Subsequently, 0.1 ml of the resulting supernatant was diluted up to 10 ml using the mobile phase. The prepared solution was then introduced into the High-Performance Liquid Chromatography (HPLC) system, and the drug peak area was carefully observed. This analytical procedure, encompassing steps [9-12], was conducted to accurately determine the content of Silodosin and Dutasteride in the marketed product, ensuring the reliability of the analysis and adherence to the specified label claims.

RESULTS AND DISCUSSION:

Development and Optimization of chromatographic condition:

Several mobile phase compositions were experimented with, and after a series of trials, the combination of methanol and water (0.1% with ortho-phosphoric acid, OPA) in a consistent ratio of 70:30 was identified as the most effective and reliable. This specific mobile phase composition was maintained consistently throughout the entire study for the chromatographic analysis. The details of these experiments, including the different mobile phase combinations tested, the observed results, and the final selection of methanol and water (0.1% with OPA) in a 70:30 ratio, are tabulated in Table 1. Additionally, the chromatographic profile resulting from this optimized mobile phase is visually represented in Figure 3. These findings collectively highlight the systematic approach undertaken to determine the most suitable mobile phase for the chromatographic study of Silodosin and Dutasteride, ensuring accuracy and consistency in the analytical methodology.

Table 1: Optimized Chromatographic conditions

Sr. No.	Instrument/Equipment	Optimized condition
1	HPLC	Agilent (S.K) Gradient System UV Detector
2	Software	Chemstation
3	Column	(Agilent C18 Column (4.6mm x 250mm)
4	Particle size packing	5 µm
5	Stationary phase	C-18 (Agilent)
6	Mobile Phase	MEOH : 0.1% OPA 70 : 30
7	Detection Wavelength	231 nm
8	Flow rate	0.7 ml/min
9	Temperature	25°C
10	Sample size	20 µl
11	pH	4
12	Run Time	10 min
13	Filter paper	0.45 µm

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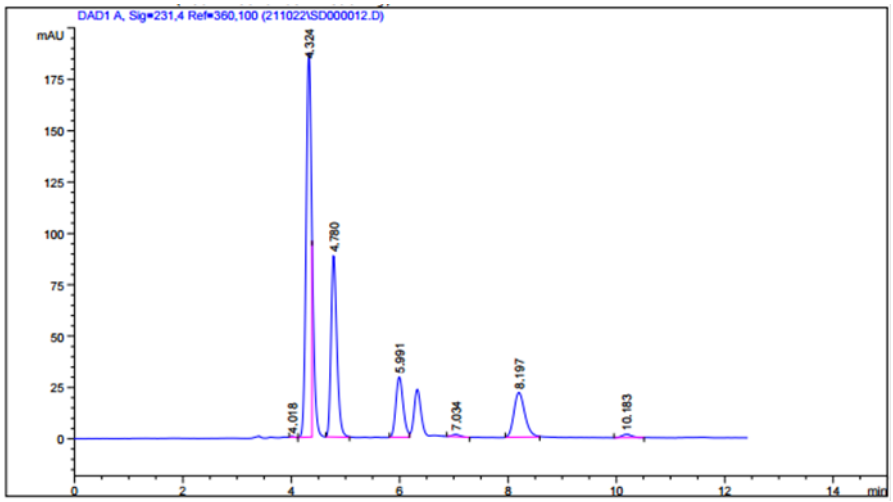

Figure 3: Standard Chromatogram of Method Development

System suitability parameters :(Ruggedness)

A comprehensive evaluation of the system suitability parameters for Silodosin and Dutasteride was conducted to assess both the resolution and reproducibility of the proposed chromatographic system. The detailed findings of this investigation are presented in Table 2. The results, as summarized in Table 2, revealed that the % RSD values were consistently below 2%. This indicates a high level of precision and reproducibility in the analytical method, underscoring the reliability of the chromatographic system for the accurate estimation of Silodosin and Dutasteride. These findings affirm the suitability of the proposed analytical approach for robust and consistent results in the quantification of these pharmaceutical compounds.

Table 2. System suitability studies on RP-HPLC for Silodosin and Dutasteride.

Method	RP-HPLC	
Drug	Silodosin	Dutasteride
Conc. (µg/ml)	80	5
Peak area	741.06	371.87
	745.11	375.95
Mean	743.09	373.92
Amount found (mg)	79.37	4.90
% Amount found	99.21	97.90
% RSD	0.39	0.77

Linearity study of Detector response:

For Silodosin, the linear relationship was explored within the concentration range of 20-100 µg/ml, while for Dutasteride, it was investigated in the range of 1.5-6.25 µg/ml. The calibration data for Silodosin and Dutasteride are comprehensively presented in Tables 2 and 3, respectively. Linear regression analysis yielded specific linear equations representing the correlation between concentrations (x) and peak areas (y). For Silodosin, the linear equation was expressed as y = 9.1186x + 19.402, while for Dutasteride, it was y = 83.313x - 34.243. The correlation coefficients for both Silodosin and Dutasteride were found to be exceptionally high, registering values of 0.999 for each compound. This indicates a strong linear correlation between peak areas and concentrations, affirming the reliability of the linear regression models. Visual representation of the calibration curves for Silodosin and Dutasteride can be observed in Figure 4 and Figure 5, respectively.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

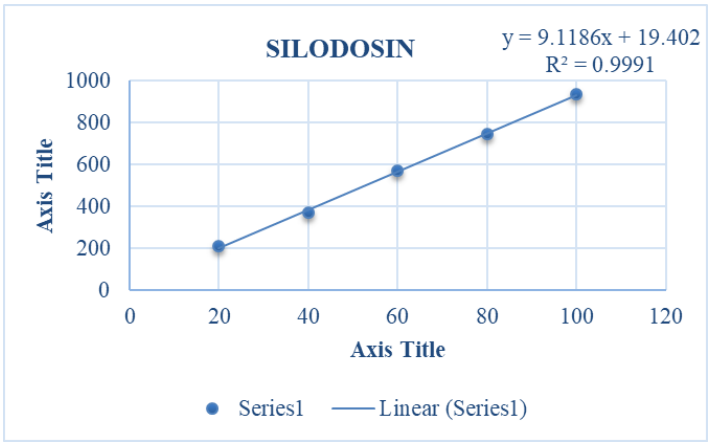

Figure 4: Calibration curve of Silodosin

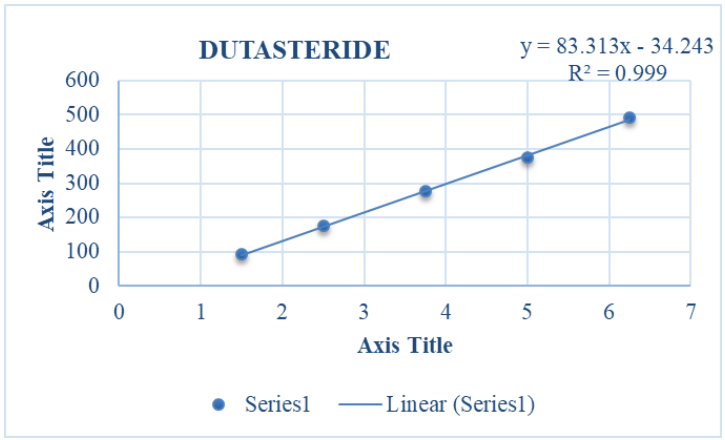

Figure 5: Calibration curve of Dutasteride.

Table 3: Linearity study of Silodosin

Sr. No	Conc	Area I	Area II	Mean	SD	%RSD
1	20	211.0247	210.6706	210.85	0.25	0.12
2	40	370.3762	369.5336	369.95	0.60	0.16
3	60	570.1991	571.1843	570.69	0.70	0.12
4	80	747.6338	746.02679	746.83	1.14	0.15
5	100	931.2217	937.311	934.27	4.31	0.46

Table 4: Linearity study of Dutasteride

Sr. No	Conc	Area I	II	Mean	SD	% RSD
1	1.5	91.7809	92.825	92.30	0.74	0.80
2	2.5	176.101	175.807	175.95	0.21	0.12
3	3.75	277.1621	274.6729	275.92	1.76	0.64
4	5	379.8449	370.42	375.13	6.66	1.78
5	6.25	492.9106	491.9423	492.43	0.68	0.14

Journal of Chemical Health Risks
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JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

Accuracy:

To validate the accuracy of the developed method, an accuracy or % recovery study was conducted for Silodosin and Dutasteride. This study involved the addition of a predetermined concentration of standard drug (at levels of 80%, 100%, and 120%) to the pre-analyzed tablet solution, followed by the analysis of the resulting recovery. The statistical validation of these recovery studies is comprehensively presented in Table 5. The accuracy of the Reverse Phase-High-Performance Liquid Chromatography (RP-HPLC) method and the spectrophotometric method was affirmed through recovery studies conducted at different concentration levels (80%, 100%, and 120%). The % recovery for both Silodosin and Dutasteride consistently fell within the range of 97.5-98.35 %. This range underscores the precision and reliability of the analytical methods, emphasizing the accuracy with which the developed method quantifies Silodosin and Dutasteride in the tablet solution.

Table 5: Result of Recovery Data for Silodosin and Dutasteride

Drug	**Silodosin**			**Dutasteride**		
Level (%)	80 %	100 %	120 %	80 %	100 %	120 %
Amount added (µg/ml)	16	20	24	1	1.25	1.5
Absorbance Mean *±S.D.	345.15 ± 0.29	381.10 ± 0.50	415.17 ± 0.001	151.34± 0.62	171.77 ± 0.72	191.84 ± 0.61
Amount recovered Mean *	15.73	19.67	23.41	0.98	1.22	1.46
% Recovery Mean *	98.29	98.35	97.53	97.75	97.83	97.59

Precision:

The methodology was established through the meticulous analysis of multiple replicates of standard solutions containing Silodosin and Dutasteride. Each solution was subjected to analysis three times to discern any potential variations within the same day (intraday) and across different days (interday). The obtained results, encapsulating the intraday and interday precision, are presented in detail in Table 6. The % RSD (Relative Standard Deviation) values, all falling below the 2% threshold, serve as crucial indicators of the precision achieved by the analytical method.

Table 6: Intraday Precision

Sr No.	Conc. µg/ml	Area I	Area II	Mean	Amt found	% Amt found	**SD**	**% SD**
Silodosin								
1	40	368.9954	366.9421	367.97	38.23	95.57	1.45	0.39
2	60	570.8379	572.3635	571.60	60.56	100.94	1.08	0.19
3	80	744.8639	743.8098	744.34	79.51	99.38	0.75	0.10
Dutasteride								
1	2.5	174.9999	173.2568	174.13	2.50	100.04	1.23	0.71
2	3.75	279.7143	278.3028	279.01	3.76	100.27	1.00	0.36
3	5	375.8107	371.8286	373.82	4.90	97.96	2.82	0.75

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

Table 7: Interday Precision

Sr No.	Conc. µg/ml	Area I	Area II	Mean	Amt found	% Amt found	SD	**% SD**
Silodosin								
1	40	372.3859	375.3713	373.88	38.88	97.19	2.11	0.56
2	60	570.7528	576.1528	573.45	60.76	101.27	3.82	0.67
3	80	743.8436	745.1136	744.48	79.52	99.40	0.90	0.12
Dutasteride								
1	2.5	173.3279	175.3379	174.33	2.50	100.14	1.42	0.82
2	3.75	279.011	280.1114	279.56	3.77	100.44	0.78	0.28
3	5	373.94	375.8146	374.88	4.91	98.22	1.33	0.35

Robustness:

To evaluate the robustness, slight variations were introduced in key method parameters. Specifically, the impact of variations in mobile phase composition and flow rate, as well as changes in wavelength, on the retention time and tailing factor of the drug peak were systematically investigated. The flow rate was adjusted by ±0.1 ml/min, and the mobile phase composition was altered to 71:29 and 69:31 proportions. Wavelength variations of ±1 nm at 232 nm and 230 nm were also examined within the optimized chromatographic conditions. The detailed results of these robustness studies are presented in Table 5, demonstrating the method's capacity to withstand these deliberate changes. Further, the robustness study involved variations in flow rate (0.6 and 0.8 ml/min), pH of the mobile phase composition (71:29 and 69:31), and wavelength (230 nm and 232 nm). The %RSD (Relative Standard Deviation) for peak area, a critical parameter, was calculated to be less than 2%, affirming the satisfactory performance of the method under these altered conditions. The collective outcomes of the robustness studies, as detailed in Table 8, contribute to the overall conclusion that the analytical method is robust and capable of delivering consistent and reliable results even when subjected to minor variations in key parameters.

Table 8: Robustness Study of Silodosin and Dutasteride.

Parameters	Conc. (µg/ml)	Silodosin Area (mean ±SD)	% RSD	Dutasteride Area (mean ±SD)	% RSD
Flow rate 0.6 ml/min	80+5	870.38 ± 1.13	0.13	328.34 ± 4.53	1.38
Flow rate 0.8 ml/min	80+5	661.71 ± 0.71	0.11	311.75± 0.65	0.31
Mobile Phase 71 + 29 ml	80+5	750.30 ± 0.63	0.08	354.70 ± 0.57	0.16
Mobile Phase 69 + 31 ml	80+5	750.78 ± 0.85	0.11	354.38 ± 1.06	0.30
Wavelength 230 nm	80+5	745.80 ± 30.59	4.10	349.60 ± 6.55	1.87
Wavelength 232 nm	80+5	775.49 ± 4.39	0.57	341.50 ± 1.18	0.59

Limit of Detection:

Table 9, presents the minimum detection limits (LOD) for Silodosin and Dutasteride. The LOD for Silodosin was established at 0.505, while for Dutasteride, it was determined to be 0.079. These LOD values signify the method's capability to accurately determine lower concentrations of both Silodosin and Dutasteride. The results emphasize the sensitivity of the developed method, validating its suitability for precise determination even at lower concentration levels.

Table 9: Limit of Detection Silodosin and Dutasteride

Silodosin	Dutasteride
Formula LOD = 3.3×avg S.D/Slope	Formula LOD = 3.3×avg S.D/Slope

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

Avg.SD = 1.4	Avg.SD = 2.01
Slope = 9.11	Slope = 83.31
LOD = 3.3 X1.4/ 9.11=0.505	LOD = 3.3 X 2.01/83.31 = 0.079

Limit of Quantitation:

Table 10, displays the minimum quantification limits for Silodosin and Dutasteride. The Limit of Quantification (LOQ) for Silodosin is established at 1.53, while for Dutasteride, it is determined to be 0.0241. These specified LOQ values confirm the method's appropriateness for the precise measurement of lower concentrations of Silodosin and Dutasteride. The outcomes substantiate the sensitivity of the developed method, affirming its reliability in the accurate determination of these substances.

Table 10: Limit of quantification Silodosin and Dutasteride

Silodosin	Dutasteride
Formula LOQ = 10×avg S.D/Slope	Formula LOQ = 10×avg S.D/Slope
Avg.SD = 1.40	Avg.SD = 2.01
Slope = 9.11	Slope = 83.31
LOD = 10 X 1.40/ 9.11 = 1.53	LOD = 10 X 2.01/83.31 = 0.241

Analysis of Marketed formulation:

The analysis of the marketed formulation containing Silodosin and Dutasteride revealed their percentage purity. The mean % assay values were calculated to be 97.78 for Silodosin and 99.78 for Dutasteride, respectively. The detailed assay results are provided in the accompanying table, while chromatograms illustrating the corresponding peaks are depicted in Figure 6.

Table 10: Assay of Marketed formulation

Conc. µg /ml	Area I	Area II	Mean	Amount Found	% Found	SD	%RSD
Silodosin							
60.00	514.939	516.167	515.55	58.67	97.78	0.868	0.168
Dutasteride							
3.75	278.587	276.121	277.35	3.74	99.73	1.744	0.629

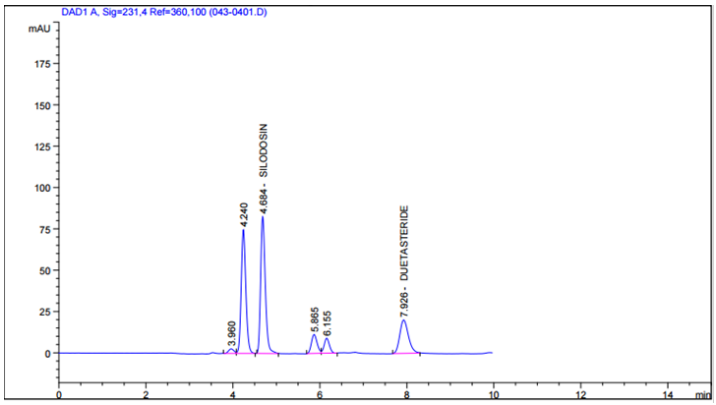

Fig 6: Chromatogram of markated formulation

Journal of Chemical Health Risks
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JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

STRESS STUDIES:

Engaging in stress testing for a drug substance is instrumental in the identification of potential degradation products, facilitating the establishment of degradation pathways and understanding the intrinsic stability of the molecule. In this context, a standardized sample containing Silodosin and Dutasteride underwent rigorous testing, including exposure to acidic, alkaline, oxidative, and hydrolytic conditions. Remarkably, the degradation observed during these stress tests adhered to the defined acceptance criteria, thereby showcasing the method's stability-indicating properties. This outcome underscores the reliability of the analytical approach in detecting and characterizing degradation products, providing valuable insights into the inherent stability of the Silodosin and Dutasteride molecules. For a more detailed comprehension of these findings, the results of stress degradation studies for Silodosin and Dutasteride are meticulously presented in tabular format. These tables serve as a comprehensive reference, illustrating the extent of degradation under each stress condition. Such information is pivotal in affirming the robustness of the drug substance and instilling confidence in its overall quality and stability.

Table 11: Forced degradation study of Silodosin

After 1 hour					
Sr. No	Degradation	Area of Standard	Area of degraded sample	Degraded up to %	% degradation
1	Acidic	369.95	343.93	92.97	7.03
2	Basic	369.95	323.36	87.41	12.59
3	H_2O_2	369.95	332.3	89.82	10.18
After 2 hours					
1	Acidic	369.95	318.66	86.14	13.86
2	Basic	369.95	303.34	81.99	18.01
3	H_2O_2	369.95	299.2	80.88	19.12
4	Neutral	369.95	365.85	98.89	1.11

Table 12: Forced degradation study of Dutasteride

After 1 hour					
Sr. No	Degradation	Area of Standard	Area of degraded sample	Degraded up to %	% degradation
1	Acidic	175.95	161.81	91.96	8.04
2	Basic	175.95	167.5	95.20	4.80
3	H_2O_2	175.95	163.69	93.03	6.97
After 2 hours					
1	Acidic	175.95	148.79	84.56	15.44
2	Basic	175.95	145.25	82.55	17.45
3	H_2O_2	175.95	141.64	80.50	19.50
4	Neutral	175.95	175.13	99.53	0.47

Conclusion:

In conclusion, the design and validation of a stability-indicating RP-HPLC method for the quantitative analysis of Silodosin and Dutasteride in various matrices, including bulk and dosage forms, as well as human plasma, have been successfully accomplished. The robustness of the developed method is evident in its ability to discern and quantify these pharmaceutical compounds under different stress conditions, affirming its stability-indicating properties. The results of the method validation, including precision, accuracy, linearity, and specificity, provide a solid foundation for its application in routine analysis. The established minimum quantification limits (LOQ) for Silodosin (1.53) and Dutasteride (0.0241) highlight the method's suitability for precise measurements, particularly in

Journal of Chemical Health Risks
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JCHR (2023) 13(6), 1741-1751 | ISSN:2251-6727

situations where lower concentrations are encountered. Moreover, the application of the validated method to both bulk and dosage forms demonstrates its versatility in pharmaceutical quality control. The extension of its utility to human plasma underscores its potential for pharmacokinetic studies and therapeutic drug monitoring. In essence, the designed and validated RP-HPLC method stands as a valuable tool for the accurate and sensitive quantification of Silodosin and Dutasteride across diverse sample types. Its successful application in both pharmaceutical and biological matrices positions it as a reliable analytical approach with broad implications for drug development, manufacturing, and clinical research.

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