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VALIDATED DISSOLUTION METHOD FOR SIMULTANEOUS ESTIMATION OF TAMSULOSIN HCL AND TADALAFIL TABLETDOSAGE FORM USING RP-HPLC

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ABSTRACT

Testing for drug dissolution is a crucial step in pharmaceutical development and continuous quality control of medication release characteristics. Drug in-vitro behaviour has been effectively described using profiles obtained from dissolution rate experiments. The current work addresses the development and validation of RP-HPLC for the detection of Tadalafil and Tamsulosin HCL in tablet and bulk drug formulations, as well as its use in in-vitro dissolving studies. Chromatography was carried on Bakerbond C18 (250 mm X4.6 ID) having particle size 5 micron the analytical coloum using Mobile phase pH 6.8 Phosphate buffer :Acetonitrile (70:30 v/v) at a flow rate 0.8 ml/min. The detection was carried out at wavelength 244 nm. Tamsulosin HCL and Tadalafil were shown to have retention times of 2.8 and 4.5 minutes, respectively. 0.1 N HCl dissolving Medium was used to analyse the dissolving pattern.A time point of 45 minutes was selected, and a USP Type I apparatus was employed with 100 RPM. For Tamsulosin HCL, the correlation coefficient was 0.9994, while for Tadalafil, it was 0.9974. Regarding linearity, accuracy, precision, robustness, ruggedness, specificity, and system applicability, the proposed approach was found to be valid. The recovery rate was determined to be between 99.63 and 101.04%. The method employed was specific for the identification and quantification of tadalafil and tamsulosin HCL in samples of dissolution and was accurate, precise, and linear over the analytical range.

INTRODUCTION

A solute dissolves in a solvent to create a solution, and this is a precise test procedure known as dissolution. Reverse phase high performance liquid chromatography is employed for the analysis of dissolution test method development.[1] The prostate and bladder, which have the highest concentrations of these receptors, are where tamsulosin HCL(TML), an alpha-1A and alpha-1B adrenoceptor antagonist, has the most significant effects. It is prescribed to treat the symptoms and indications of benign prostatic hyperplasia. Better urine flow is made possible by the detrusor muscles in the bladder and the smooth muscles in the prostate relaxing as a result of antagonistic interactions between these receptors. Other alpha-1 adrenoceptor antagonists produced in the 1980s were less selective and more prone to act on blood vessel smooth muscle, causing hypotension.Tamsulosin HCL has the IUPAC name 5-[(2R)-2-[2-(2-ethoxy phenoxy) ethyl]aminopropyl] 2-Methoxybenzene-1-sulfonamidehydrochloride Hydrochloride with the the chemical formula is C20H29ClN2O5S, and the molecular weight is 444.97 gm/mol.[2] The molecular structure of the drug is given in **Fig1.**

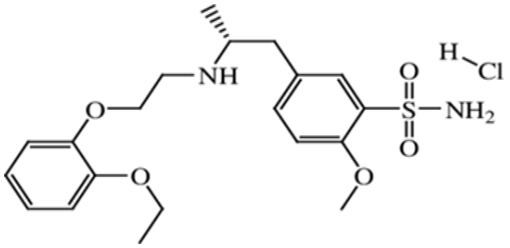


Fig 1: Structure of Tamsulosin HCL

Tadalafil (TDF) is a phosphodiesterase 5 inhibitor used for the treatment of erectile dysfunction, benign prostatic hyperplasia, and pulmonary arterial hypertension. Tadalafil is a phosphodiesterase-5 inhibitor that treats erectile dysfunction (ED), pulmonary arterial hypertension (PAH), and benign prostatic hypertrophy.The IUPAC Name of the Tadalafil (2R,8R)-2-(2H-1,3-benzodioxol-5-yl)-6-methyl- 3,6,17 triazatetracyclo [8.7.0.0^{3,8}. 0^ {11,16}]heptadeca-1(10),11,13,15tetraene-4,7-dione with molecular weight- 389.404 gm/mol and molecular formula $C_{22}H_{19}N_3O_4$.[3] The molecular structure of the drug is give in **Fig .2**

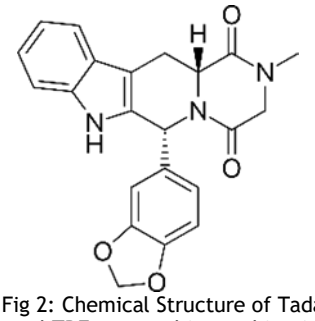


Fig 2: Chemical Structure of Tadalafil

TML and TDF are used in combination treatment to treat benign prostatic hyperplasia and erectile dysfunction. The combination of both medications has been found to be more effective than either treatment alone.Various UV[4-7], HPTLC[8-13], HPLC[14-20], and spectroflurometry[21] methods have been documented in the literature for individual or mixed dose forms. The current study describes the development and validation of an analytical technique for estimating Tamsulosin HCL and Tadalafil in pharmaceutical dose using RP-HPLC. The suggested approach has been optimised and validated in accordance with the ICH Guidelines.[22-23]

MATERIAL AND METHOD:

Instruments

The chromatographic process was carried out using an Agilent Technologies UPLC system, a variable wavelength programmable UV identifier, and a Rheodyne injector with a 20l fixed circle. A Bakerbond C18 (250 mm X4.6 ID) having particle size 5 micron analytical coloum was used. Individual Wenser High Precision Balance Model: PGB 100 electronic equilibrium were used for Spectrophotometric judgements and gauging.

Material: Agilant HPLC was used. Tamsulosin HCL and Tadalafil were obtain from pharma tech solution Nashik. The combination dose of the marketed formulation of drug procured from the local market of brand CONTIFLO-T (SUN Pharmaceutical Industries Ltd). All the chemical used are HPLC & AR grade and were obtain from Merk SpecialitiesPvt Ltd,Mumbai and Labogens.

Preparation of stock solution:

Accurately Weighed and transferred 4 mg Tamsulosin HCL and 5 mg Tadalafil working Standards into a 100ml clean dry volumetric flask, added 3/4th volume of diluent, sonicated for 5 minutes, and made up to final volume with diluents. Tamsulosin HCL has a final concentration of 4 µg/mL, whereas Tadalafil has a concentration of 50 µg/mL. These medications' working standard solutions were created by dilution of the relevant stock solution with mobile phase.

Preparation of Mobile Phase A(pH 6.8 Phosphate buffer):

Solution I: Dilute 1000.0 ml of water with 13.87 g of potassium dihydrogen phosphate.

Dissolve 35.08 g of disodium hydrogen phosphate in water and dilute to 1000.0 ml with the same solvent.Sonication was used to degas the mobile phase after it was filtered via a 0.45m membrane filter.

Preparation of Mobile Phase B: 100 % ACN

Optimized Dissolution Test:

Six Contiflo-T tablets were used in the experimental dissolving technique, which was carried out in a USP type I apparatus. The dissolving media had a 900 ml capacity, and stirring was done at 50, 75, and 100 rpm. The medium's temperature was fixed at 37±5°C. The withdrawn sample was 5 ml, and it was sampled for 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 minutes. This procedure preserved the washbasin state. The removed sample was analysed by HPLC at 244 nm after being filtered using Whatman No. 41 filter paper. Results are displayed in **Table 1**

Table 1: Optimized Chromatographic Conditions

Mobile phase	0.2 M Phosphate buffer : Acetonitrile
Selection of column	Bakerbond C18 (4.6mm x 250mm, Particle size: 5µm)
Injection volume	20 ml
Flow rate	1.0 ml/min
Column Temperature	Room Temperature
Detection Wavelength	244 nm
Run Time	7 minutes
Retention time	Tamsulosin HCL (2.8 min) and Tadalafil (4.5 min)

Method Validation[22-23]

Linearity

As demonstrated by the steady baseline, the chromatographic conditions were established using the optimised parameters, and the mobile phase and stationary phase were given time to equilibrate. Different concentrations of test solutions were independently injected, and the chromatograms were captured. Using a stock solution containing TML (4 µg/mL) and TDF (50 µg/mL), respectively, in five 10 ml volumetric flasks, a series of test preparations of TML and TDF were made. The final volume was then brought up to the required level using mobile phase. Under the ideal chromatographic conditions, a volume of 20µ l from each concentration was injected into the HPLC three times.

Accuracy

In accordance with ICH rules, known API quantities were added to the 900 ml dissolving medium at various levels, including 50%, 100%, and 150%. A total of 10 pills were added, with pure TML dosages of 0.4, 0.8, and 1.2 mg, TDF dosages of 5, 10, and 15 mg, and two Contiflo-T pills with a 0.4/5 mg strength. For each level with concentrations of 1.2 µg/mL, 1.6 µg/mL, and 2 µg/mL of TML and 15 µg/mL, 20µ g/mL, and 25 µg/mL of TDF, respectively, 9 ml of sample was further extracted and diluted up to 10 ml. The recoveries of each of these samples are determined after analysis. For this study three dilutions of each 50 %, 100 % and 150 % level prepared and injected in to the chromatography.

Precision

The 900ml dissolving media was supplemented with a specified amount of API (TML 4 mg and TDF 50 mg). The intraday precision investigation was carried out by creating 10 ml test solutions of the same concentration by removing stock solutions of 0.9, 2.7, and 4.5 ml and analysing it three times a day. To establish interday precision for both medicines, the identical approach was used on three different days. The outcome was given as %RSD. With a percent relative standard deviation smaller than 2, the precision result demonstrated acceptable repeatability.

Robustness

The effect of a tiny purposeful change in the optimised procedure was investigated using robustness evaluation. To assess the robustness of the suggested approach, parameters were purposefully altered. These characteristics included flow rate and pH variations. The factor chosen was altered at two levels: flow rate in ml/min and pH. Significant changes in peak regions and decreased variability in retention duration were noted.

Ruggedness

Ruggedness is the investigation of the influence of external factors on the approach. To assess the robustness of the suggested approach, parameters were purposefully altered. These factors included system variation, various analysts, and

atmospheric fluctuations. The 900ml dissolving media was supplemented was generated by extracting 2.7 ml of solution from the dissolving media and diluting it up to 10 ml according to the test procedure before being injected into an HPLC system with a flow rate of 1.0 ml/min by two distinct analyzers.

System Suitability

To validate the system, technique, and column performance, system suitability characteristics were examined. The test solution was made by taking 2.7 ml of solution from the dissolving medium and diluting it up to 10 ml. TML and TDF standard solutions were injected into the system six times, and system suitability parameters were verified

RESULT AND DISCUSSION

High performance liquid chromatographic method was developed and validated for determination of Tamsulosin HCL and Tadalafil in bulk and dosage form. Mobile phase consisted of 0.2 M Phosphate Buffer: Acetonitrile (70:30 v/v). Chromatogram obtained shows maximum response at 244 nm shown in **Fig.3.**

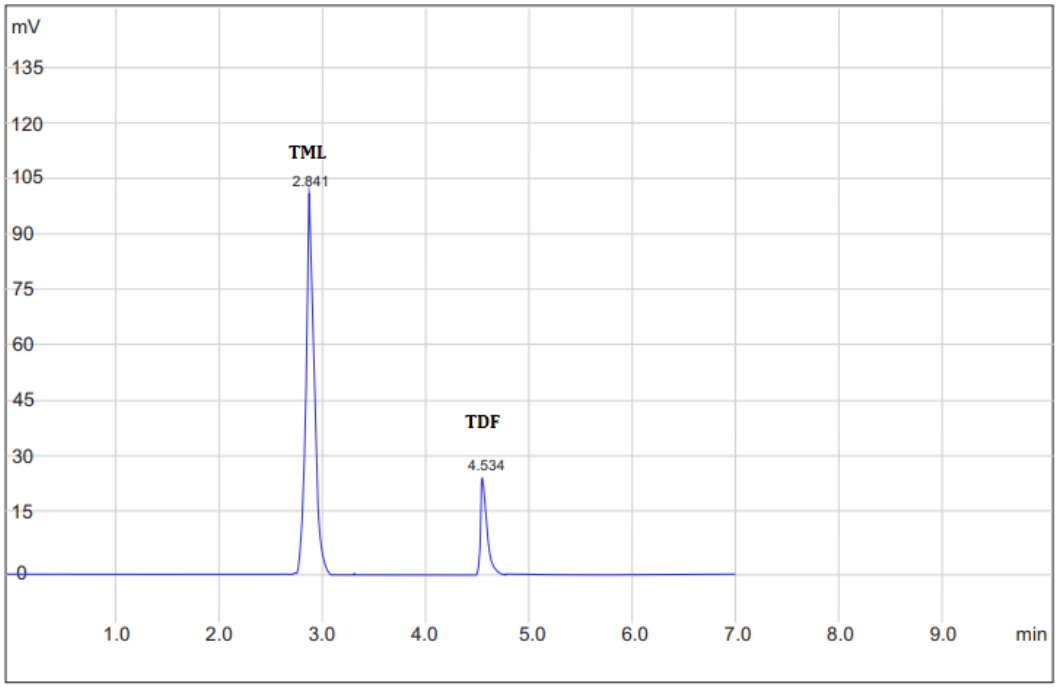


Fig.3: Chromatogram of TML and TDF

T

he IR study of pure drug was carried out by using Fourier transform infrared spectrophotometer (BRUKER). Infrared absorption spectrum of Tamsulosin HCLand Tadalafil was recorded and interpreted over the wave number 4000 to 600 cm^{-1}using Fourier Transform spectrophotometer (Bruker, ECO- ATR) as shown in **Fig.4** and **Fig.5**

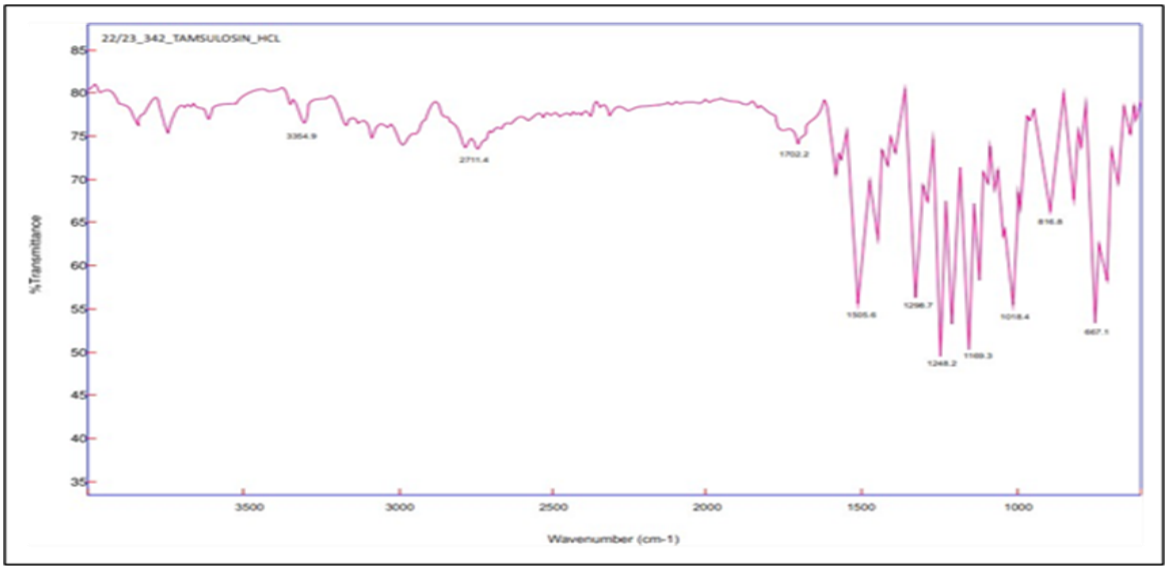
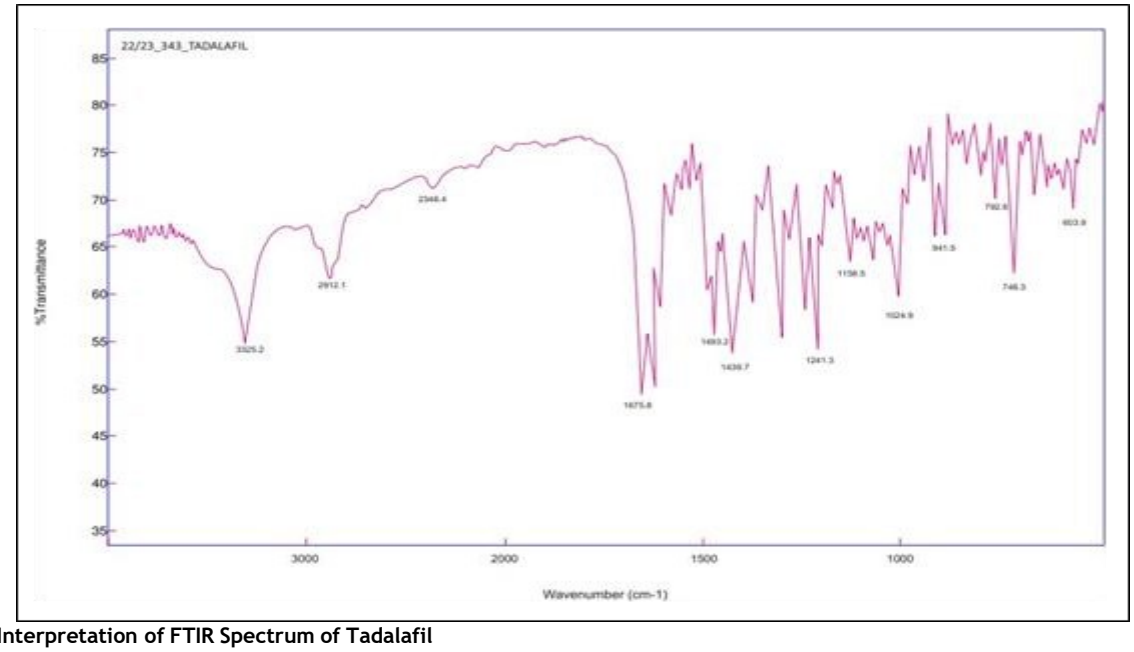


Fig .4: IR Spectrum of Tamsulosin HCL

Fig.5: IR Spectrum of Tadalafil

Table 3:

Sr. No.	Functional group	Standard range(cm-1)	Observed range(cm1)
1	N-H Bending	3400-3250	3354.9
2	C=C Stretching	1550-1450	1505.6
3	S=O stretching	1350-1200	1298.7
4	C-O stretch	1300-1250	1248.2
5	C-S Stretch	700-650	667.1



Interpretation of FTIR Spectrum of Tadalafil

Sr. No.	Functional group	Standard range(cm-1)	Observed range(cm-1)
1	N-H Stretching	3300-3400	3325.02
2	C-H stretch Strong	2900-2980	2904.55
3	N=C=O Stretch(Isocynide)	2300-2350	2344.80
4	C=O stretch	1600-1700	1677.49
5	C-H Bending	1400-1450	1438.02

Determination of Sink Condition

1.2 mg TML and 15 mg TDF was added into different dissolution media. Greater solubility was observed in 0.1 N HCl as shown in **Table 4**

Table 2: Interpretation FTIR Spectrum of Tamsulosin H

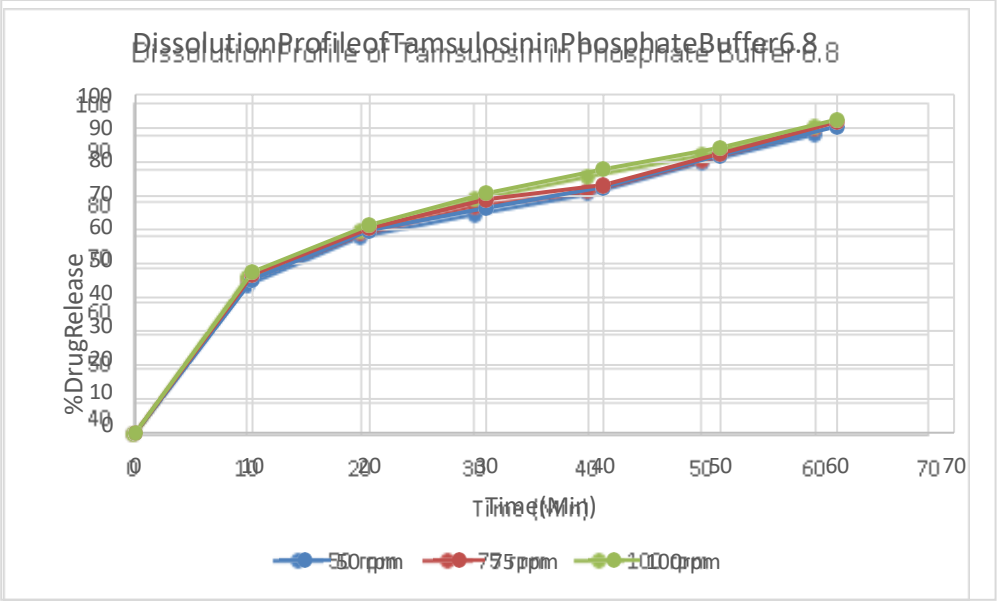
Table 4:Determination of Sink Condition

Dissolution Media	Drugs	Mg added	Mg found	%Dissolution
Water	TamsulosinHCL	1.2	0.31	25.83
	Tadalafil	15	2.9	19.33
Phosphate buffer 6.8	TamsulosinHCL	1.2	1.12	93.33
	Tadalafil	15	14.8	98.67
0.1NHCL	TamsulosinHCL	1.2	1.19	99.17
	Tadalafil	15	14.9	99.33

Optimization of Dissolution Profile

According to the solubility study of Tamsulosin HCL and Tadalafil with the suitable sink conditions determines which is the best dissolution medium (phosphate buffer pH 6.8 or 0.1 N HCl). The dissolution study results shown in **Fig.6,Fig.7,Fig.8,Fig.9**

Fig 6: Dissolution profile of Tamsulosin HCL in Phosphate Buffer 6.



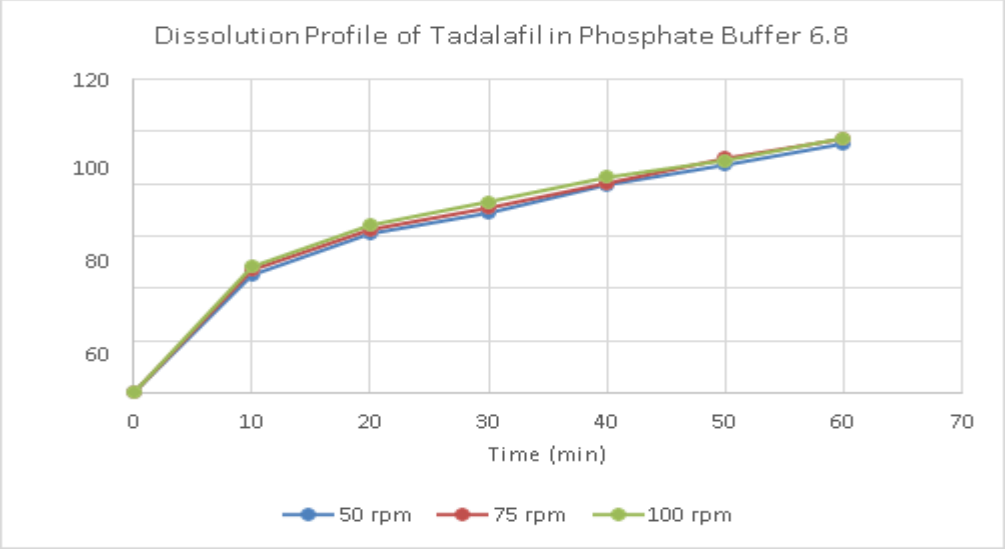


Fig 7: Dissolution profile of Tadalafil in Phosphate Buffer 6.8

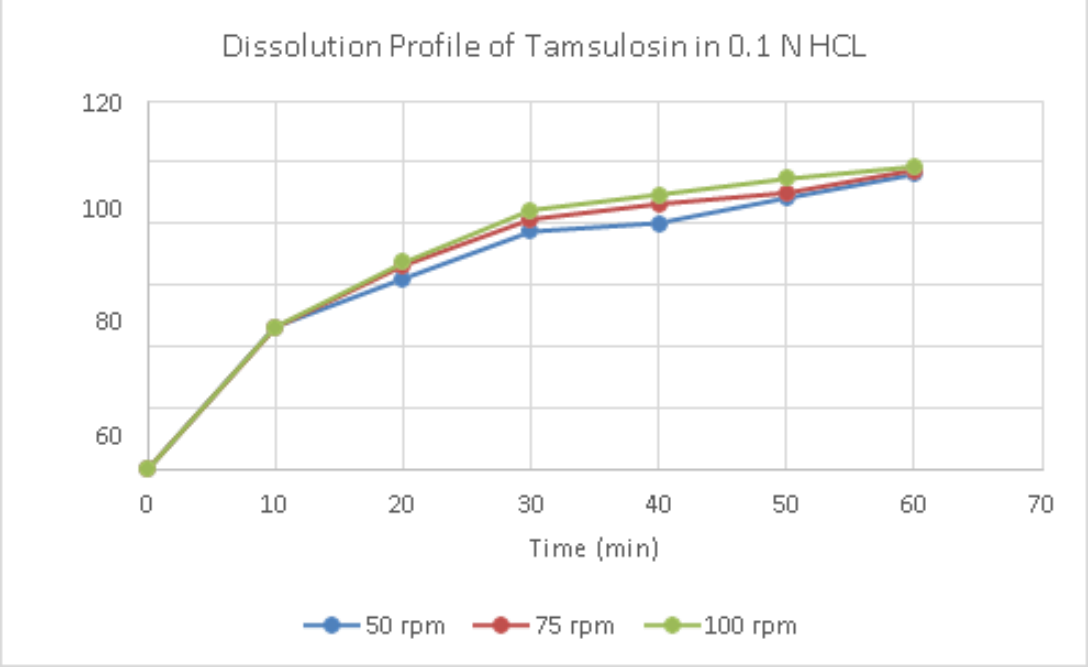


Fig. 8: Dissolution profile of Tamsulosin HCL in 0.1 N HCL

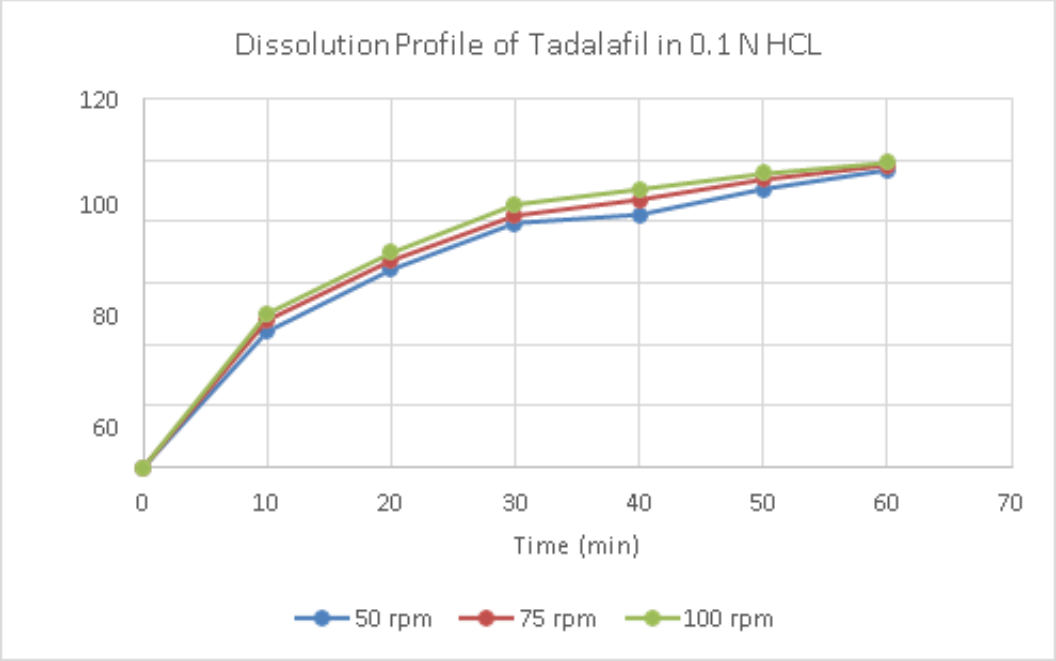


Fig 9: Dissolution profile of Tadalafil in 0.1 N HCL

From the dissolution Study it was clearly observed that Dissolution of drugs are pH dependent and as the pH increases dissolution rate also increases.The suitable dissolution condition for Tamsulosin HCL and Tadalafil was 900 ml of 0.1 N HCL as dissolution media at 37^0C , USP type I apparatus with stirring speed of 100 rpm at 45 min.The dissolution profile is as shown in **Table 5.**

Table 5: DissolutionProfile of Tamsulosin HCLand Tadalafilin 0.1NHCL at 100 RPM

Time(min)	TamsulosinHCL(%)	Tadalafil(%)
0	0	0
10	46.5	50.1
20	67.4	69.8
30	84.5	85.5
40	89.5	90.4
50	94.7	95.6
60	98.6	99.1

OPTIMIZED METHOD FOR DISSOLUTION:
Dissolution parameters
Dissolution Medium: 0.1 N HCL
Volume: 900 Ml
Apparatus: USP type I (Basket)
RPM: 100
Temperature: 37^0C
Time Point: 60 min
METHOD VALIDATION:
Accuracy :

The accuracy was investigated using the conventional addition method, and the percentage recovery discovered was within an acceptable range. In each stage, three determinations were made. Individual and mean recovery rates were both more than 85%. As a consequence, the proposed method's accuracy was established and shown to the smart recovery values. Results of recovery study are shown in **Table 6**

Table 6: Data for recovery study

Level of addition	% Mean recovery*		SD		% RSD	
	TML	TDF	TML	TDF	TML	TDF

50%	100.78	100.08	0.44	0.59	0.43	0.58
100%	99.91	99.74	0.30	0.38	0.30	0.39
150%	99.86	100.08	0.14	0.85	0.14	0.85

Precision

Precision within and between days ensures that test findings are repeatable. TML and TDF both have % RSD values less than 2.

Table 7 displays the intraday and interday precision results.The % RSD was determined to be less than 2, indicating that the findings are within the standards.

Table 7: Precision studies(Intra-day and Inter-day)

Drug	Conc. [µg/mL]	Intra- day Amount found [µg/mL]		Inter- day Amount found [µg/mL]	
		SD [n= 3]	% RSD	SD [n= 3]	% RSD
TML	0.4	6864.20	0.36	18366.31	0.95
	1.2	21270.92	0.35	5383.28	0.09
	2.0	22625.03	0.23	24093.27	0.24
TDF	5	3623.10	0.84	1173.93	0.27
	15	38717.67	3.05	9166.58	0.71
	25	16419.74	0.81	22364.74	1.10

Robustness:

Robustness was investigated using various purposeful alterations in chromatographic settings, such as changes in flow rate and wavelength. The TML and TDF were determined to have a 2% RSD from the robustness analysis. As a result, it is strong and adheres to ICH criteria.. Results are shown in **Table 8**.

Table 8: Data for Robustness study of TML and TDF

Sr.No	Parameter	TML		TDF	
		SD	%RSD	SD	% RSD
1	Change in Flow rate (ml/min)	13922.75	0.23	10562.86	0.82
2	Change in PH	34071.56	0.57	12442.07	0.96

Ruggedness:

Various analysts analysed ruggedness. RSD was shown to be less than 2% in the Tamsulosin HCL and Tadalafil studies. TML yielded values of 100.15% and 99.89%, respectively.TDF yielded 99.89% and 99.95% results, respectively.As a result, it adheres to ICH requirements..

Specificity

Excipients and impurities were not interacting with the standard drugs. Hence method is specific.

System Suitability

To validate the system, technique, and column performance, system suitability characteristics were examined. Tamsulosin HCL and Tadalafil standard solution were injected into the system five times, and system suitability characteristics were verified.Results are shown in **Table 9.**

Table 9: Data for System suitability study

System Suitability Parameters	TML	TDF
Retention time (T_R)	2.84 min	4.55 min
Capacity factor (K ')	0.96	1.11
Theoretical plate (N)	9850	9632
Tailing factor (T)	1.14	1.08
Asymmetry factor	0.70	0.37

CONCLUSION

The current study was a successful attempt to determine TML and TDF in bulk and dosage form dissolution methods utilising HPLC. The approach was created through experimentation and a review of the literature. The proposed method's simplicity, speed, repeatability, and economy perfectly meet the goal of this study endeavour.

For the simultaneous estimate of TML and TDF, the Dissolution technique was designed and verified. The mobile phase was composed of 0.2M Phosphate Buffer: Acetonitrile, which is both simple to make and inexpensive. The sample recoveries obtained in the formulation are satisfactory. According to the dissolving profile, the optimal dissolution medium is 900 ml 0.1 N HCL utilising a USP type 1 apparatus with a speed of 100 rpm at 370C and a sample withdrawal time point of 45 minutes. The approach was discovered to be simple, linear, quick, accurate, precise, repeatable, and robust. The % RSD was found to be within the ICH standards. The results demonstrated that the suggested Dissolution technique was appropriate for the accurate, precise, and quick simultaneous determination of TML and TDF in bulk and pharmaceutical dose form.

According to the ICH criteria, all of the validated parameters exhibited acceptable results with appropriate correlation co-efficients and <% RSD.

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