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Development and Validation of Ultra Performance Liquid Chromatographic Method Simultaneous Estimation of Aspirin and Ticlopidine Hydrochloride in Pharmaceutical Formulation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The combined dose tablet formulation containing aspirin and ticlopidine hydrochloride is used to reduce the formation of harmful blood clots in blood vessels which helps in preventing a heart attack or stroke in people with heart disease. The objective of the present work was to develop an accurate, precise, economical and less time consuming UPLC method and subsequently validate the method as per ICH guidelines, for routine quality control of combined dose tablet formulation containing above mentioned drug.
Methods: The present work describes development and validation of ultra performance liquid chromatographic method for simultaneous quantitation of aspirin and ticlopidine hydrochloride in tablets. The chromatographic separation was carried out using Supelcosil LC-18 (3.3 cm × 4.6 mm

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× 3 µm) column using mixture of Potassium Phosphate buffer (0.01M) and Acetonitrile (20:80 v/v) as mobile phase with a flow rate of 0.6 ml per minute, total run time was 3 minutes. The detection and quantitation of chromatographic peaks was carried out at 230 nm.

Results: The retention time for aspirin (ASP) and ticlopidine hydrochloride (TPH) was 0.529 minutes and 1.530 minutes, respectively. The linearity of detector response was observed in the concentration range of 20 – 60 µg/ml and 50-150 µg/ml for ASP and TPH, respectively. The LOD and LOQ for ASP and TPH was found to be 0.399 & 1.209 and 3.385 & 10.260, respectively. The accuracy of the method was found in the range of 99.92 – 100.58 % and 98.91 – 100.52 for ASP and TPH, respectively. The relative standard deviation for intra-day and inter-day precision studies was below 2 % indicating that the method is precise. The robustness of the proposed method was evaluated by varying the chromatographic parameters and the effect of these changes on retention time and tailing factor was studied. The % RSD for retention time and tailing factor was below 2 % indicating that the method is robust. The forced degradation studies were carried out to evaluate the specificity of the method. As the method was able to quantitate ASP and TPH selectively in presence of degradation products, the method was found to be specific. As the results of validation studies were within standard limits, the method was successfully applied for simultaneous estimation of ASP and TPH in marketed tablet formulation.

Conclusion: The method has distinct advantages over reported UV and HPLC methods and hence the developed UPLC method can be used for routine quality control of Aspirin and Ticlopidine hydrochloride combined tablet formulation.

Keywords: UPLC; aspirin; ticlopidine hydrochloride; method development; validation; International Conference on Harmonization (ICH) Q2R1.

1. INTRODUCTION

Aspirin (ASP), chemically 2-(acetyloxy)-salicylic acid acetate [1], has anti-inflammatory and antipyretic properties and acts as an inhibitor of cyclooxygenase which result in the inhibition of the biosynthesis of prostaglandins. Aspirin also inhibits platelet aggregation and is used in the prevention of arterial and venous thrombosis. Ticlopidine hydrochloride, chemically 5-(2-chlorobenzyl)-4, 5, 6, 7-tetrahydro-thieno [3, 2-c]pyridine monohydrochloride [2], is an effective inhibitor of platelet aggregation. The drug has been found to significantly reduce infarction size in acute myocardial infarcts and is an effective antithrombotic agent in arteriovenous fistulas, aorto-coronary bypass grafts, ischemic heart disease, and venous thrombosis. The combination of these two antiplatelet medicines is used to reduce the formation of harmful blood clots in blood vessels which helps in preventing a heart attack or stroke in people with heart disease.

Literature survey revealed variety of analytical methods for estimation of aspirin alone or in combination with other drugs such as Spectrophotometry [3-5], HPLC [6-9], HPTLC [10-12] etc. Ticlopidine is also reported to be analyzed by spectrophotometry [13], HPLC [14], UPLC [15] etc. alone or in combination with other drugs. Few derivative spectroscopy [16] and HPLC [17] methods are reported for simultaneous estimation of Aspirin and Ticlopidine hydrochloride in pharmaceutical formulation. There is no UPLC method reported for simultaneous quantitative analysis of Aspirin and Ticlopidine hydrochloride in pharmaceutical formulation. UPLC has several advantages over HPLC and HPTLC such as shorter run time, low solvent consumption, fast analysis while maintaining compounds resolution and column efficiency. Hence, an attempt has been made to develop and validate UPLC method for simultaneous estimation of aspirin and ticlopidine hydrochloride in pharmaceutical formulation. As the method is economical and less time consuming as compared to the reported methods, it can be used as an alternative to the reported methods for simultaneous estimation of aspirin and ticlopidine hydrochloride in combined dose tablet formulation.

2. REAGENTS AND CHEMICALS

Aspirin and Ticlopidine hydrochloride pure drugs were obtained as gift samples from Sai Life Sciences Ltd., Pune, and RPG Life Sciences Ltd., Mumbai, respectively. HPLC grade methanol and was used for column washing and for preparation of diluent. Double distilled water was used for column washing and for preparation of phosphate buffer. HPLC grade potassium dihydrogen orthophosphate was used for

preparation of buffer. HPLC grade Orthophosphorice acid was used to adjust pH of diluent. Combined dose tablet formulation "Doprin plus" manufactured by Lifecare Innovation Ltd. was procured from the local pharmacy store.

3. METHODS

3.1 Preparation of Diluent

Diluent-I: Adjust the pH of methanol to 2.0 by adding ortho phosphoric acid in 1000.0 ml of methanol
Diluent-II: Potassium Phosphate buffer (0.01M) and Acetonitrile (50:50 v/v).

3.2 Preparation of Standard Stock Solution

- **Stock Solution A**: Accurately weighed quantity (10.0 mg) of Aspirin (ASP) was transferred to 10.0 ml volumetric flask, dissolved and diluted up to the mark with diluent-I. The solution was filtered through NNSY25 0.22µm nylon filter (Concentration: 1000 µg/ml).
- **Stock Solution B:** Accurately weighed quantity (10.0 mg) of Ticlopidine hydrochloride (TPH) was transferred to 10.0 ml volumetric flask, dissolved and diluted up to the mark with diluent-I. The solution was filtered through NNSY25 0.22µm nylon filter(Concentration: 1000 µg/ml)
- **Stock Solution C:** An accurately weighed quantity of ASP (10.0 mg) and TPH (25.0 mg) was transferred to 25.0 ml volumetric flasks, dissolved and diluted up to mark withdiluent-I. From this solution, 1.0 ml was transferred to 10.0 ml volumetric flask and diluted to the mark with diluent-II. The solution was mixed and filtered through NNSY25 0.22µm nylon filter (Concentration:40 µg/ml ASP and 100 µg/ml TPH, respectively).

3.3 Selection and Optimization of Chromatographic Parameters

Standard stock solution A, B, and C were injected in to Supelcosil LC-18 (3.3cm×4.6mm×3µm) column and chromatographed using different solvents with varying proportions and at different flow rates in order to determine the best conditions for the effective separation of ASP and TPH with acceptable system suitability parameters. The chromatograms were evaluated at 230 nm as both the drugs showed signification absorption at this wavelength. Some of the solvent combinations used as mobile phase resulted in poor peak symmetry and low resolution. However, the mobile phase containing Potassium Phosphate buffer (0.01M) and Acetonitrile (20:80 v/v), and flow rate 0.6 ml/min showed good resolution, peak shape and desired elution time. Hence, the mixture Potassium Phosphate buffer (0.01M) and Acetonitrile (20:80 v/v) was selected further chromatographic analysis.

3.4 System Suitability Parameters

To ascertain resolution and reproducibility of proposed chromatographic system for estimation of ASPI and TICL in tablets, system suitability parameters like tailing factor (T), resolution (R), column efficiency (number of theoretical plates, N), and system precision were studied.

Standard stock solution C containing ASP (40 µg/ml) and TCP (100 µg/ml) was used for analysis. Six replicate injections of standard solution were injected into the column and chromatographed using optimized chromatographic conditions.

3.5 Study of Linearity Range

Aspirin: Aliquot portions of standard stock solution A, were appropriately diluted with mobile phase to obtain final concentration of 10, 20, 30, 40, 50, and 60 µg/ml respectively. The diluted solutions were filtered through 0.2µ membrane filter.

Ticlopidine hydrochloride*:* Aliquotportions of standard stock solution B, were appropriately diluted with mobile phase to obtain final concentration of 25, 50, 75, 100, 125, and 150 µg/ml, respectively. The diluted solutions were filtered through NNSY25 0.22µm nylon filter.

Then each solution (1.0 µl) was injected into the column and chromatographed using optimized chromatographic conditions. The corresponding chromatograms were recorded and area of each peaks for ASP and TCP were measured at 230 nm. Each sample solution was chromatographed in triplicate and the mean peak area for ASP and TCP was calculated. The standard calibration curves of mean peak areas versus concentration were plotted for both ASP and TCP.

3.6 Assay of Marketed Formulation

Standard solution: Standard stock solution C was used for analysis.

Sample solution: Twenty tablets were weighed average weight was calculated and crushed to obtain fine powder. Accurately weighed quantity of tablet powder equivalent to about 40 mg of ASP and 1000 mg of TCP was transferred to 50.0 ml volumetric flask, 25 ml diluent-I was added and ultrasonicated for 10 min, volume was then made up to the mark. The resulting solution was mixed and filtered through NNSY25 0.22µm nylon filter. The filtrate was appropriately diluted with diluent-II so as to obtain a final concentration within linearity range, and filtered using 0.2 µ membrane filter.

Equal volumes of standard stock solution C and sample solution (1.0 µl) were injected into the column and chromatographed using optimized chromatographic conditions. The corresponding chromatograms were recorded and area of each peak for ASP and TCP was measured at 230 nm. Each solution was injected and chromatographed in triplicate. Amount of ASP and TCP in sample (in mg) was calculated by comparing the mean peak area of sample with that of standard. Amount of drug estimated in mg/tablet was calculated using following formula,

> Amount of drugs estimated in mg/tablet = PAspl/PAstd. X Wstd(mg)/Dfstd. X Dfspl/Wspl(g) X Avg. Wt. of Tablet (g).

Where, PAspl is mean peak area of sample, PAstd is mean peak area of standard, Wstd (mg) mean weight of standard in milligrams, Dfstd is dilution factor for standard, Dfspl is dilution factor form sample, Wspl (g) weight of tablet powder sample in gram, Avg. Wt. (g) mean average weight of tablet in gram.

The percent label claim was then calculated using amount of drug estimated in mg/tablet and the label claim of marketed formulation.

4. METHOD VALIDATION

The method was validated as per ICH guidelines as follows,

4.1 Accuracy

To ascertain the accuracy of proposed method, recovery studies were carried out by standard addition method at three different levels viz. 80%, 100% and 120% of test concentration.

An accurately weighed quantity of pre-analysed tablet powder equivalent to about 40 mg ASPI and 100 mg TICL was transferred in 50.0 ml volumetric flasks. To the flask added 32 mg/80 mg, 40 mg/100 mg, 48 mg/120 mg of ASP/TCP pure drug for 80%, 100% and 120% level of recovery respectively. Extraction was performed using diluent-I and dilutions with diluent-II. The solution was diluted to obtain final concentration within linearity range. Solutions were prepared in triplicate at each level of recovery and analysed. The accuracy was determined and expressed as percent recovery.

4.2 Precision

The intra-day precision of the proposed method was evaluated by analyzing the tablet formulation at different time intervals on same day i.e., morning afternoon and evening. However, the inter-day precision was evaluated by analyzing the tablet formulation on three consecutive days. The samples were analyzed in similar manner as discussed in analysis of marketed formulation. The results of precisions studies was expressed in terms of percent relative standard deviation.

4.3 Robustness

Robustness of the proposed method was evaluated by small but deliberate variations in the chromatographic parameters such as change in flow rate (± 0.1 ml) and composition of mobile phase (± 1 ml), The effect of these changes on the retention time and tailing factor or the drug peaks was evaluated by calculating the percent relative standard deviation.

4.4 Ruggedness

Ruggedness of the proposed method was evaluated by performing the analysis of tablet formulation by three different analysts using same instrument. The analysis of marketed formulation was done in duplicate by each analyst. The results expressed in terms of percent relative standard deviation of the estimated percent label claim.

4.5 LOD & LOQ

The LOD and LOQ were separately determined based on the standard deviation of response of the calibration curve. The standard deviation of

y- intercept and slope of the calibration curves were used to calculate the LOD and LOQ.

4.6 Forced Degradation Study

Amount of tablet powder equivalent to about 20 mg ASP was separately transferred to six different 25.0 ml volumetric flasks (Flask No. 1, 2, 3, 4 and 5), added 5.0 ml of 0.1 N HCl, 0.1 N NaOH and 3 % H_2O_2 to Flask No. 1, 2 and 3, respectively. Contents of flask No. 1, 2, and 3 were heated in water bath for 6h at 80^0C. Flask No. 4 containing tablet powder was kept at 60^0C for 24 h to study the effect of heat on tablet sample (heat degradation). For neutral hydrolysis 5.0 ml of water was added to flask No. 5 and heated in water bath at 80^0C for 6h. The forced degradation was performed in the dark to exclude the possible degradative effect of light. Flask No. 6 containing a tablet powder sample was exposed to UV radiations at 254 nm for 24 h. Samples were withdrawn at appropriate times and subjected to LC analysis after suitable dilution to evaluate the ability of the proposed method to separate ASP & TCP peak from its degradation products.

5. RESULTS AND DISCUSSION

5.1 Optimization of Chromatographic Conditions

After several trials, the following chromatographic conditions were selected for chromatographic separation as quantitation of ASP and TCP:

- **Column :** Supelcosil LC-18 (3.3cm× 4.6mm×3µm)
- **Mobile phase :** Potassium Phosphate buffer (0.01M) and Acetonitrile (20:80 v/v)
- **Flow rate :** 0.6 ml/min
- **Detection Wavelength :** 230 nm
- **Sample injection volume :**1 µl
- **Run Time :** 3.0 min.

The chromatogram of standard solution obtained under the optimized chromatographic conditions is depicted in Fig. 1. The retention time of ASP and TCP was found to be 0.529 minutes and 1.530 minutes, respectively.

5.2 System Suitability Parameters

To ascertain the suitability of the proposed method, the system suitability parameters were studied and the results obtained are as follows,

5.3 Linearity

The correlation coefficient for the calibration curves for both ASP and TCP were found to be 0.996 indicating good linear relationship between the peak area and the concentration range under study i.e., 10 - 60 µg/ml and 25 – 150 µg/ml for ASP and TCP, respectively. The linearity curves for ASP and TCP are depicted in Fig. 2 and Fig. 3, respectively.

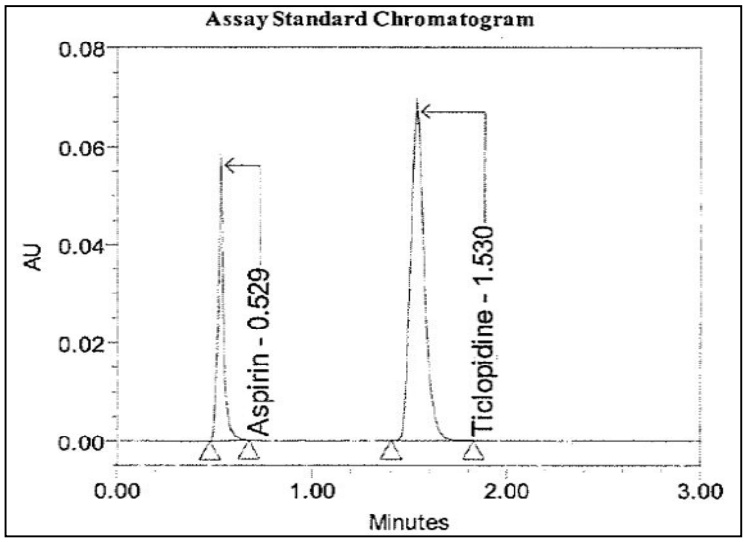

Fig. 1. Typical Chromatogram of Aspirin (RT = 0.52 min) and Ticlopidine hydrochloride (RT=1.53 min)

Table 1. Results of system suitability parameters

Sr. No.	Parameter	ASP	TCP
1.	Resolution (R)	5.19	
2.	Tailing factor (T)	1.21	1.33
3.	No. of theoretical plates (N)	2286	2282
4.	% RSD for peak area (System precision)	0.29	0.76

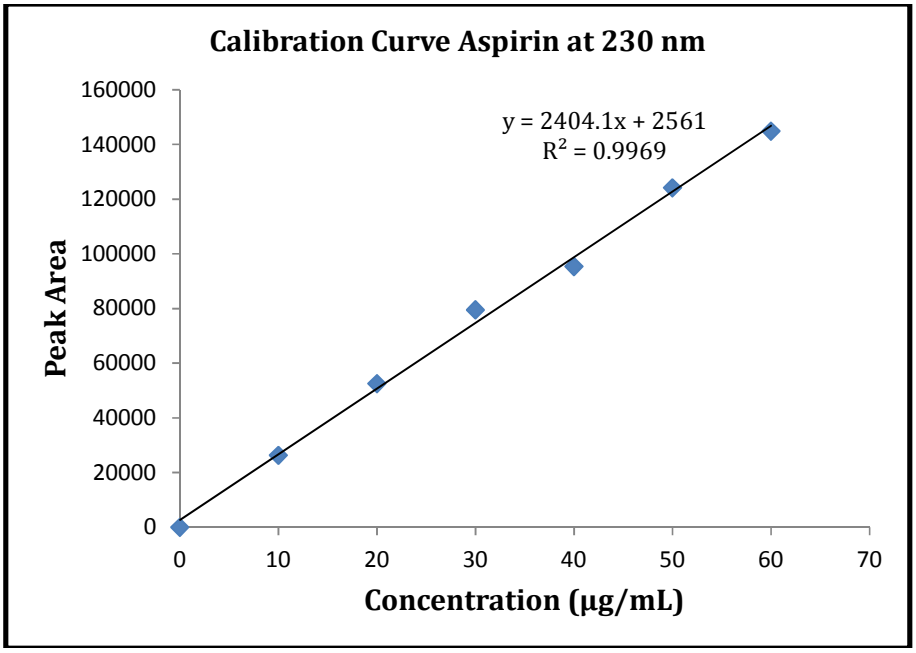

Fig. 2. Calibration Curve for Aspirin at 230 nm

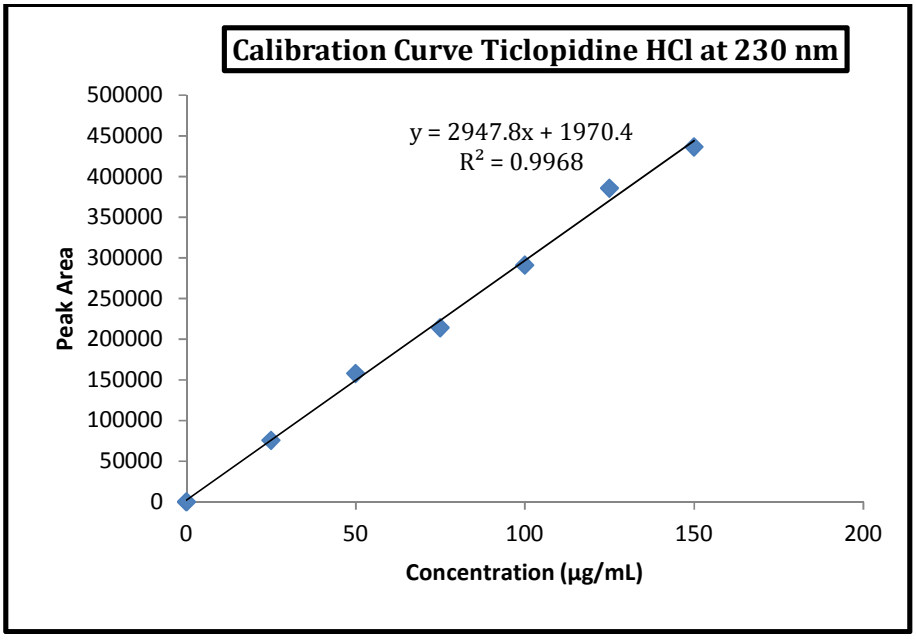

Fig. 3. Calibration Curve for Ticlopidine hydrochloride at 230 nm

5.4 Assay of Marketed Formulation

The assay of marketed formulation "Doprin Plus" containing Aspirin (40 mg) and Ticlopidine hydrochloride (100 mg) was carried out by proposed method and the results were expressed in amount of drug estimated in mg/tablet and percent label claim. The results are depicted in Table 2. The percent label claim estimated by the proposed method was in the range of 99.78–101.87 % and 99.38–99.92% for Aspirin and Ticlopidine hydrochloride, respectively. The method was able to selectively quantitate aspirin and ticlopidine hydrochloride in presence of excipients.

5.5 Method Validation

5.5.1 Accuracy

The percentage recovery at three levels (80%, 100% and 120% of test concentration) was found in the range of 98.72–101.70% and 98.21–101.30% for aspirin and ticlopidine hydrochloride, respectively. The results of recovery studies are depicted in Table 3. As the results of percent recovery are within the acceptable limits, the method is considered to be accurate.

5.5.2 Precision

Repeatability (intra-day precision) and intermediate precision (inter-day precision) of the developed method was expressed in terms of relative standard deviation (RSD) of percent label claim estimated. The results of percent label claim and standard deviation of set of results was less than 2 % for both the drugs indicating the precision of the developed method (Table 4).

5.5.3 Ruggedness and Robustness

The results of ruggedness study, evaluated by analyzing tablet formulation by three different analysts (in duplicate) using same instrument, was expressed as standard deviation of the percent label claim estimated. The standard deviation was found to be less than 2 indicating the ruggedness of proposed method. Robustness of the proposed method was studied by small but deliberate variations in the optimized method parameters. The effect of change in flow rate and mobile phase ratio on retention time and tailing factor were studied. Results of robustness studies are shown in following Table 5. The standard deviation for retention time and tailing factor obtained under varying chromatographic conditions was less than 2 indicating the robustness of the method.

5.5.4 LOD & LOQ

The LOD and LOQ for ASP was found to be 1.121 µg/mL and 3.385 µg/mL, respectively. For TCP the LOD and LOQ were found to be 3.419 µg/mL and 10.260 µg/mL, respectively.

5.5.5 Forced degradation study

Both Aspirin and Ticlopidine HCl were found to be degrade under alkaline, oxidiezed, thermal and neutral stress conditions. However, both the drugs were stable in acid and photo-degradation stress conditions. The method was able to selectively quantitate Aspirin and Ticlopidine hydrochloride in presence of degradation products indicating the specificity of the developed method.

Table 2. Results of analysis of marketed formulation

Brand Name: Doprin Plus		Label Claim: ASP-100 mg; TCP-250 mg.					
Sr. No.	Weight of tablet powder taken (mg)	Peak Area*		Amount of drug estimated (mg/tablet)		% Label Claim	
		ASP	TCP	ASP	TCP	ASP	TCP
1.	205.2	110446	329464	100.01	246.30	100.68	99.20
2.	205.2	113775	331087	100.8	246.51	101.87	99.38
3.	205.2	112111	330276	100.20	246.44	100.23	99.36
4.	205.2	110385	331953	99.96	247.71	99.78	99.52
5.	205.3	110380	332341	99.85	248.05	101.64	99.65
6.	205.1	110375	332147	99.78	247.85	100.15	99.92

** denotes average of three determinations*

Table 3. Results of accuracy study

Sr. No.	Level of recovery	Amount of drug added (mg)		Amount of drug recovered (mg)		% Recovery		Mean Percent Recovery		SD (±)	
		ASP	TCP	ASP	TCP	ASP	TCP	ASP	TCP	ASP	TCP
	80 %	32.1	80.2	32.33	80.35	100.72	100.19	99.92	98.91	±0.831	±1.110
1.		32.2	80.1	31.90	76.59	99.06	98.21				
		32.1	80.0	31.27	78.66	99.97	98.33				
2.	100 %	40.1	100.3	41.01	100.21	101.55	99.91	100.51	99.56	±0.900	±0.466
		40.1	100.1	40.09	99.13	99.97	99.03				
		40.0	100.1	40.01	99.84	100.01	99.74				
3.	120 %	48.1	120.0	49.07	120.25	101.70	100.21	100.58	100.52	±1.620	±0.680
		48.2	120.3	47.58	121.87	98.72	101.30				
		48.0	120.0	47.17	120.06	101.31	100.05				

Table 4. Results of precision study

Intra-day Precision			
Drug	**% Label claim***	**S. D.**	**C. V.**
ASP	98.83	± 0.600	0.607
TCP	100.52	± 0.810	0.805
Inter-day Precision			
ASPI	99.06	± 1.365	1.377
TCP	99.60	± 1.209	1.213

Table 5. Results of robustness study

Factor	Level	Retention time		Tailing factor	
Flow Rate (ml/min)		**ASP**	**TCP**	**ASP**	**TCP**
0.5	– 0.1	0.62	1.83	1.15	1.06
0.6	0	0.53	1.52	1.12	1.07
0.7	+ 0.1	0.44	1.31	1.13	1.08
	S.D	**± 0.240**	**± 0.925**	**± 0.015**	**± 0.010**
Mobile Phase Ammonium acetate buffer:ACN (v/v)		**ASP**	**TCP**	**ASP**	**TCP**
19:81	– 1.0	0.51	1.51	1.01	1.09
20:80	0	0.53	1.52	1.03	1.06
21:79	+1.0	0.55	1.56	1.02	1.07
	S.D	**± 0.245**	**± 0.856**	**± 0.980**	**± 1.422**

6. CONCLUSION

The proposed UPLC method for simultaneous estimation of Aspirin and Ticlopidine hydrochloride was found to be selective, sensitive, accurate, precise, reproducible, economical and less time consuming as compared to the reported methods. Hence, the proposed UPLC method can be employed for routine quality control of Aspirin and Ticlopidine hydrochloride in combined dose tablet formulation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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