Journal of Pharmaceutical and Biomedical Analysis 52 (2010) 160–165

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

# A validated stability-indicating normal phase LC method for clopidogrel bisulfate and its impurities in bulk drug and pharmaceutical dosage form

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ARTICLE INFO

*Article history:*
Received 15 October 2009
Received in revised form
14 December 2009
Accepted 19 December 2009
Available online 28 December 2009

*Keywords:*
Development
Normal phase liquid chromatography
Clopidogrel bisulfate
Impurities
Stability-indicating

ABSTRACT

A novel stability-indicating normal phase liquid chromatographic (NP-LC) method was developed for the determination of purity of clopidogrel drug substance and drug products in bulk samples and pharmaceutical dosage forms in the presence of its impurities and degradation products. This method is capable of separating all the related substances of clopidogrel along with the chiral impurities. This method can be also be used for the estimation of assay of clopidogrel in drug substance as well as in drug product. The method was developed using Chiralcel OJ-H (250 mm × 4.6 mm, 5 μm) column. n-Hexane, ethanol and diethyl amine in 95:5:0.05 (v/v/v) ratio was used as a mobile phase. The eluted compounds were monitored at 240 nm. Clopidogrel bisulfate was subjected to the stress conditions of oxidative, acid, base, hydrolytic, thermal and photolytic degradation. The degradation products were well resolved from main peak and its impurities, proving the stability-indicating power of the method. The developed method was validated as per International Conference on Harmonization (ICH) guidelines with respect to specificity, limit of detection, limit of quantification, precision, linearity, accuracy, robustness and system suitability.



## 1. Introduction

Clopidogrel is a potent anti-platelet and anti-thrombotic drug. It is a dihydro thieno pyridine derivative pro-drug which is inactive *in vitro*. *In vivo*, it selectively and irreversibly inhibits the binding of adenosine diphosphate (ADP) to its platelet receptors [1]. Although the majority of the drug is hydrolyzed by esterase to an inactive carboxylic acid metabolite, the full anti-aggregating activity of the drug is achieved by biotransformation to 2-oxo-clopidogrel by cytochrome P450-1A. This intermediate metabolite is hydrolyzed and generates an active form which reacts as thiol reagent with the ADP receptor on platelets thus preventing the binding of ADP. Clopidogrel has an absolute S-configuration; the corresponding R-enantiomer is totally devoid from anti-aggregating activity [2]. The carboxylic acid metabolite and R-enantiomer are listed by the United States Pharmacopeia (USP) as impurities A and C in the monograph, besides impurity B which is a racemic mixture of regioisomer of clopidogrel (impurities B1 and B2) [3]. A glycoprotein-based ovomucoid column is being used in the USP pharmacopoeial method. The resolution of impurities B1 and B2 from clopidogrel is going bad in less number of injections in the USP method. Apart from the monograph listed impurities, impurites D and E were included in this study. Fig. 1 shows the structures of clopidogrel bisulfate and its five impurities.

Few other methods have been reported for the estimation of clopidogrel by spectrophotometric [4,5], LC [6,7], CZE [8] and TLC [9] methods. A bio-analytical method for the determination of clopidogrel in plasma using LC–MS/MS was reported [10]. Clopidogrel was determined by LC in the presence of its impurities using a chiral column and its impurities were determined at low levels [11]. The carboxylic acid metabolite (impurity A) was determined in human plasma by GC–MS [12], by LC with UV detection [13] and by LC–MS [14]. The major objective of the present work is to develop a single method for the separation of chiral and non-chiral impurities of clopidogrel bisulfate in drug substance and drug product. The same method was used for the estimation of assay of the drug substance and drug product. Further the use of carbohydrate-based chiral HPLC column ensures the column life unlike glycoprotein-based columns. No LC method was reported in European Pharmacopeia. So far to our knowledge there was no method has been reported using normal phase chromatography.

## 2. Experimental

### 2.1. Chemicals and reagents

Tablets and standards of clopidogrel bisulfate and its five impurities namely impurity A (98.1%), impurity B (98.2%) (racemic mixture of B1 and B2), impurity C (99.2%), impurity D (99.1) and

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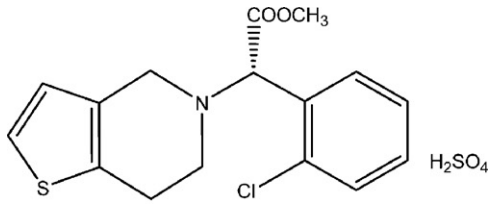
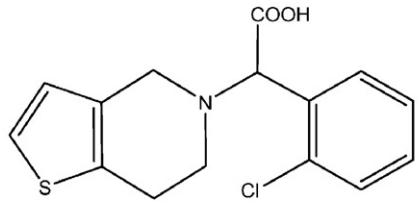
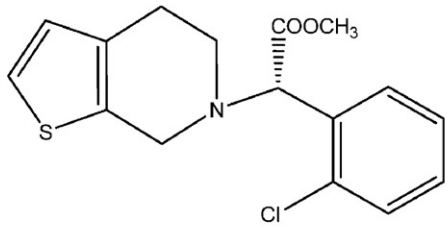
doi:10.1016/j.jpba.2009.12.027



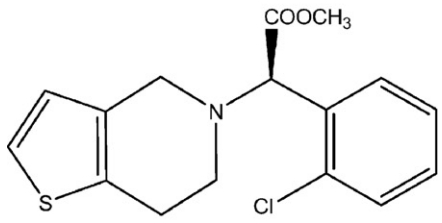

Clopidogrel bisulfate




Impurity-A (USP Related compound A)




Impurity-B (USP Related compound B)

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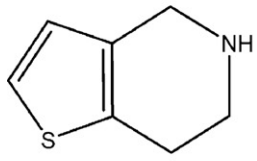
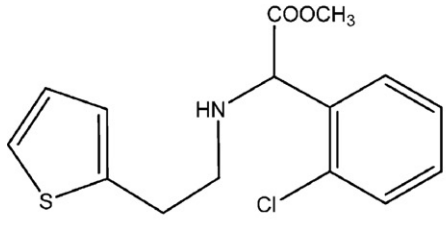



Impurity-D




Impurity-E

**Fig. 1.** Structures of clopidogrel bisulfate and its five impurities.

impurity E (98.4) were supplied by Dr. Reddy's Laboratories Limited, Hyderabad, India. The HPLC grade n-hexane, ethanol and analytical grade diethyl amine were purchased from Merck, Darmstadt, Germany. High purity water was prepared by using Millipore MilliQ Plus water purification system (Millipore, Milford, MA, USA).

### 2.2. Equipment

The Waters HPLC system (Waters, Milford, USA) used consists of a pump, auto sampler and a PDA detector. The output signal was monitored and processed using empower-2 software. Cintex digital water bath was used for hydrolysis studies. Photo stability studies were carried out in a photo stability chamber (Sanyo, Leicestershire, UK). Thermal stability studies were performed in a dry air oven (Cintex, Mumbai, India).

### 2.3. Chromatographic conditions

The method was developed using Chiralcel OJ-H (250 mm × 4.6 mm, 5 μm) column. n-Hexane, ethanol and diethyl amine in 95:5:0.05 (v/v/v) ratio was used as mobile phase. The mobile phase was filtered through a nylon membrane (pore size 0.45 μm) filter. The flow rate of the mobile phase was 1.0 ml/min. The column temperature was maintained at 25 °C and the wavelength was monitored at 240 nm. The injection volume was 10 μl.

### 2.4. Preparation of stock solutions

A stock solution of clopidogrel (2.0 mg/ml) was prepared by dissolving appropriate amount of clopidogrel bisulfate drug in ethanol. Working solutions of 1000 and 100 μg/ml in mobile phase were prepared from the above stock solution for the related substance determination and assay determination, respectively. A stock solution of impurity (mixture of impurities A–E) at 0.5 mg/ml was also prepared in ethanol.

### 2.5. Preparation of sample solution

Twenty clopidogrel bisulfate 75 mg tablets were weighed, transferred to a clean and dry mortar and ground into a fine powder. Tablet powder equivalent to 200 mg drug was then transferred to a 100 ml volumetric flask, 70 ml of ethanol was added, and the flask was attached to a rotary shaker for 10 min to disperse the material completely. The mixture was then sonicated for 10 min and diluted to volume with ethanol to give a solution containing 2000 μg/ml. This solution was centrifuged at 3000 rpm for 5 min and supernatant was diluted using mobile phase to give test solutions containing 1000 and 100 μg/ml. These solutions were filtered through a 0.45 μm pore size Nylon 66 membrane filter.

### 2.6. Method validation

The proposed method was validated as per ICH guidelines [15].

#### 2.6.1. Specificity

Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities [16]. The specificity of the developed LC method for clopidogrel was carried out in the presence of its impurities namely impurity A–E. Stress studies were performed for clopidogrel bisulfate tablets to provide an indication of the stability-indicating property and specificity of the proposed method. Intentional degradation was attempted with a stress condition of UV light (254 nm), heat (60 °C), acid (0.5N HCl), base (0.5N NaOH) and oxidation (3.0% $H_2O_2$) to evaluate the ability

of the proposed method to separate clopidogrel from its degradation product. For heat and light studies, study period was 10 days whereas for hydrolytic, acid, base and oxidation, it was 24 h. Peak purity test was carried out for the clopidogrel peak by using PDA detector in stress samples.

Assay of stressed samples was performed by comparison with qualified reference standard and the mass balance (% assay + % impurities + % degradation products) was calculated.

#### 2.6.2. Precision

The precision of the related substances method verified by repeatability and by intermediate precision. Repeatability was checked by injecting six individual preparations of clopidogrel bisulfate real sample (75 mg tablets) spiked with 0.20% of its five impurities (0.20% of impurities with respect to 1.0 mg/ml of clopidogrel). % RSD of area for each impurity was calculated. The intermediate precision of the method was also evaluated using different analyst and performing the analysis on different days.

Precision of assay method was evaluated by carrying out six independent assays of real sample of clopidogrel at 0.1 mg/ml level against qualified reference standard. The intermediate precision of the assay method was evaluated by different analysts.

#### 2.6.3. Limits of detection (LOD) and quantification (LOQ)

LOD and LOQ for impurities A, B, C, D and E were determined at a signal-to-noise ratio of 3:1 and 10:1, respectively, by injecting a series of dilute solutions with known concentrations [15]. Precision study was also carried out at LOQ level by injecting six individual preparations of impurities and calculating the % RSD of the area.

#### 2.6.4. Linearity

Linearity test solutions for the assay method were prepared from clopidogrel stock solution at six concentration levels from 50 to 150% of assay analyte concentration (50, 75, 100, 125 and 150 μg/ml). The peak area versus concentration data was treated by least-squares linear regression analysis.

Linearity test solutions for the related substance method were prepared by diluting stock solution to the required concentrations. The solutions were prepared at six concentration levels from LOQ to 150% of the specification level (LOQ, 0.075, 0.15, 0.20, 0.25 and 0.30%).

#### 2.6.5. Accuracy

Accuracy of the assay method was evaluated in triplicate using three concentration levels 50, 100 and 150 μg/ml on real sample (75 mg tablets). Standard addition and recovery experiments were conducted on real sample to determine accuracy of the related substance method. Study was carried out in triplicate using four concentration levels LOQ, 0.5, 1.0 and 1.5 μg/ml. The percentages of recoveries for clopidogrel and its impurities were calculated.

#### 2.6.6. Robustness

To determine the robustness of the developed method, experimental conditions were deliberately altered and the resolution between clopidogrel and its impurities and tailing factor for clopidogrel and its impurities were recorded. The flow rate of the mobile phase was 1.0 ml/min, to study the effect of flow rate on the resolution, flow was changed by 0.1 units from 0.9 to 1.1 ml/min. The effect of the column temperature on resolution was studied at 20 and 30 °C instead of 25 °C. The effect of the percent ethanol strength on resolution was studied by varying ethanol by −3 to +3% while other mobile phase components were held constant as stated in Section 2.3.

#### 2.6.7. Solution stability

Solution stability of clopidogrel in the assay method was carried out by leaving both the test solutions of sample and reference standard in tightly capped volumetric flasks at room temperature for 48 h. The same sample solutions were assayed for 12-h interval up to the study period.

Solution stability of clopidogrel and its impurities in the related substance method was carried out by leaving spiked sample solutions in tightly capped volumetric flasks at room temperature for 48 h. Content of impurities A–E were determined for every 12-h interval up to the study period.

## 3. Results and discussion

### 3.1. Method development and optimization

The main objective while developing this method was to have a single method for separation of impurities A, D, E along with the separation of impurity B, enantiomer of impurity B and enantiomer of clopidogrel (impurity C) from clopidogrel. As the separation demands the resolution of chiral and non-chiral impurities together, chiral stationary phases based on carbohydrate like cellulose and amylose were chosen as first choice. Initially the separation was attempted in reverse phase. None of the reverse phase-based chiral columns were able to separate all the impurities. Finally Chiralcel OJ-H was found to be showing separation of all impurities in normal phase mode using hexane and ethanol in mobile phase. Chiralcel OJ-H is a silica column with the coating of cellulose tris(4-methyl benzoate). Addition of little amount of diethyl amine as basic modifier improved the peak shape resulting in further increase in resolution of impurities. The mobile phase composition was fixed as n-hexane, ethanol and diethyl amine in 95:5:0.05 (v/v/v) ratio with an isocratic elution. The flow rate of the mobile phase was fixed as 1.0 ml/min.

Mobile phase was chosen as the diluent, as the blank chromatogram was clean without any interference with analyte peak and the impurity peaks. Also no interference from the excipients was observed. Under optimized conditions clopidogrel and its five impurities were well separated with resolution greater than 2.0; typical retention times were approximately 21.93, 4.88, 10.87, 16.34, 12.99, 8.78, 19.64 min for clopidogrel, impurity A, impurity B1, impurity B2, impurity C, impurity D and impurity E; respectively.

System suitability parameters were evaluated for clopidogrel and its five impurities. Tailing factor for all five impurities and clopidogrel was found to be less than 1.3. Resolution of clopidogrel and its five potential impurities was greater than 3.0 for all pairs of compounds.

### 3.2. Results of forced degradation studies

Clopidogrel was found to degrade significantly in acid hydrolysis and in base hydrolysis and mild degradation was observed in thermal stress conditions leading to the formation of impurity A (Fig. 2). This was confirmed by co-injecting impurity A to these degraded samples. Clopidogrel was found to be stable under photolytic degradation, hydrolytic and oxidation conditions. Photodiode array detector was employed to check and ensure the homogeneity and purity of clopidogrel peak in all the stressed sample solutions.

Assay studies were carried out for stress samples against clopidogrel qualified working standard. The mass balance (% assay + % impurities + % degradants) results are presented in Table 1. The purity and assay of clopidogrel was unaffected by the presence of its impurities and degradation products and thus confirms the stability-indicating power of the developed method.

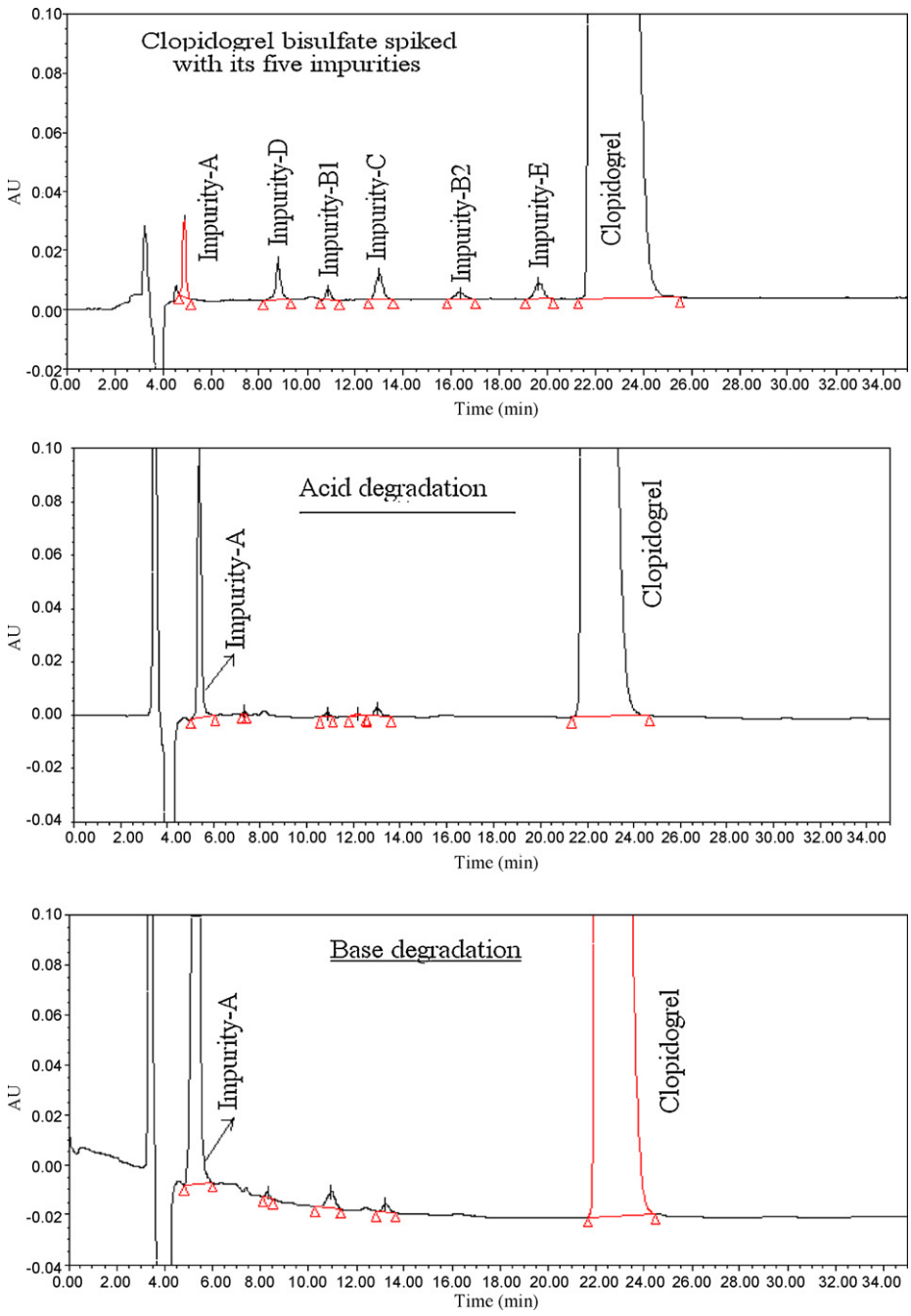



**Fig. 2.** Typical chromatograms of clopidogrel bisulfate spiked with its five impurities and its forced degradation samples.

**Table 1**
Summary of forced degradation studies.

| Stress condition | % impurities formed | | | | | | % Assay | Mass balance |
|---|---|---|---|---|---|---|---|---|
| | A | B (B1 + B2) | C | D | E | Total impurities | | |
| Oxidative degradation | 0.21 | ND | 0.05 | ND | ND | 0.6 | 98.6 | 99.2 |
| Acid degradation | 6.22 | ND | 0.08 | ND | ND | 7.1 | 92.2 | 99.3 |
| Base degradation | 12.15 | ND | 0.03 | ND | ND | 12.8 | 86.1 | 98.9 |
| Hydrolytic degradation | 0.15 | ND | 0.04 | ND | ND | 0.5 | 98.6 | 99.1 |
| Thermal degradation | 0.32 | ND | 0.35 | ND | ND | 1.3 | 98.2 | 99.5 |
| Photolytic degradation | 0.11 | ND | 0.02 | ND | ND | 0.2 | 99.6 | 99.8 |

ND: not detected.

**Table 2**
Regression and precision data.

| Parameter | Clopidogrel | Impurity A | Impurity B | Impurity C | Impurity D | Impurity E |
|---|---|---|---|---|---|---|
| LOD (μg/ml) | 0.012 | 0.016 | 0.014 | 0.009 | 0.011 | 0.013 |
| LOQ (μg/ml) | 0.032 | 0.041 | 0.032 | 0.031 | 0.036 | 0.036 |
| Regression equation ($y$) | | | | | | |
| Slope ($b$) | 10,651 | 68,9479 | 27,8588 | 51,9493 | 90,5366 | 68,8696 |
| Intercept ($a$) | 93,892 | −7213 | 1694 | −5254 | −4910 | −3773 |
| Correlation coefficient | 0.9999 | 0.9992 | 0.9999 | 0.9991 | 0.9995 | 0.9989 |
| Standard error | 64,428.0 | 3072.9 | 3085.1 | 439.2 | 2488.3 | 3491.5 |
| Significance of intercept | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero |
| Significance of slope | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero | Significantly different from zero |
| Lack-of-fit | No evidence against lack-of-fit | No evidence against lack-of-fit | No evidence against lack-of-fit | No evidence against lack-of-fit | No evidence against lack-of-fit | No evidence against lack-of-fit |
| Precision (% RSD) | 0.81 | 1.53 | 2.11 | 1.64 | 1.44 | 1.93 |
| Intermediate precision (% RSD) | 0.75 | 1.29 | 2.62 | 1.61 | 1.91 | 2.72 |

Linearity range is LOQ—150% with respect to 1.0 mg/ml of clopidogrel for impurities. Linearity range is 50–150% with respect to 0.1 mg/ml of clopidogrel for assay.

**Table 3**
Evaluation of accuracy.

| Amount spiked[a] | % recovery[b] | | | | | |
|---|---|---|---|---|---|---|
| | Clopidogrel | Impurity A | Impurity B | Impurity C | Impurity D | Impurity E |
| LOQ | 98.2 ± 1.51, 1.22 | 98.1 ± 0.32, 5.98 | 98.5 ± 0.22, 7.06 | 98.9 ± 0.33, 3.44 | 99.1 ± 0.35, 2.56 | 99.3 ± 0.18, 3.78 |
| 50% | 100.8 ± 0.35, 2.20 | 99.1 ± 0.28, 3.12 | 98.1 ± 0.23, 8.32 | 98.5 ± 0.11, 13.77 | 100.5 ± 0.15, 3.34 | 99.9 ± 0.37, 0.21 |
| 100% | 100.3 ± 0.27, 1.22 | 97.5 ± 0.42, 6.16 | 99.9 ± 0.33, 0.28 | 100.1 ± 0.17, 0.42 | 99.5 ± 0.23, 2.26 | 98.6 ± 0.39, 3.60 |
| 150% | 100.5 ± 0.33, 1.46 | 99.1 ± 0.28, 3.41 | 102.1 ± 0.36, 5.74 | 98.7 ± 0.45, 2.83 | 98.9 ± 0.29, 4.03 | 100.5 ± 0.19, 2.54 |

[a] Amount of five impurities spiked with respect to 0.20% specification level individually to 0.5 mg/ml of clopidogrel.
[b] Mean ± % RSD, a Student's $t$-test value comparing the recovery with reference value 100%. Student's $t$-test showed no significant differences between mean recovery and reference value 100% at $n = 3$, df = 2, $p = 0.01$.

### 3.3. Validation of the method

#### 3.3.1. Precision

The % RSD of assay of clopidogrel during the assay method precision study was 0.81% and the % RSD for the area of impurities A–E in related substance method precision study was within 2.11%. The % RSD of the assay results obtained in the intermediate precision study was within 0.75% and the % RSD for the area of impurities A–E were well within 2.62%, conforming good precision of the method. The % RSD values are presented in Table 2.

#### 3.3.2. Limits of detection and quantification

The determined limit of detection, limit of quantification and precision at LOQ values for clopidogrel and its five impurities were reported in Table 2.

#### 3.3.3. Linearity

Linearity calibration plot for the assay method was obtained over the calibration ranges tested, i.e. 50–150 μg/ml and correlation coefficient obtained was greater than 0.999. The result shows that an excellent correlation existed between the peak area and concentration of the analyte. Linear calibration plot for the related substance method was obtained over the calibration ranges tested, i.e. LOQ to 0.30%. The correlation coefficient obtained was greater than 0.998. The above result shows that an excellent correlation existed between the peak area and the concentration of impurities A–E.

#### 3.3.4. Accuracy

The percentage recovery of clopidogrel from drug product was ranged from 98.2 to 100.5%. The percentage recovery of impurities in clopidogrel samples varied from 97.5 to 102.1%. The % recovery values for impurities and clopidogrel are presented in Table 3.

#### 3.3.5. Robustness

In all the deliberate varied chromatographic conditions (flow rate, column temperature and composition of organic solvent), the resolution between all pairs of compounds was greater than 2.0 and tailing factor for clopidogrel and its impurities was less than 1.2. The assay variability of clopidogrel was within ±1%. The variability in the estimation of clopidogrel bisulfate impurities was within ±10%.

#### 3.3.6. Solution stability

The % RSD of the assay of clopidogrel during solution stability experiments were within 1%. No significant changes were observed in the content of five impurities during solution stability experiments. The solution stability experiment data confirms that the sample solutions used during assay and the related substance determination were stable for 48 h.

## 4. Conclusions

The simple isocratic normal phase LC method developed for quantitative analysis of clopidogrel and related substances in bulk samples and pharmaceutical dosage forms is precise, accurate, linear, robust and specific. Satisfactory results were obtained from validation of the method. The method is stability-indicating and can be used for routine analysis of production samples and to check the stability of samples of clopidogrel bisulfate in bulk drugs and in pharmaceutical dosage forms.

## Acknowledgement

The authors wish to thank the management of Dr. Reddy's Laboratories Ltd. for supporting this work. We thank Mr. Lakshmi Narayana (Daicel India, Hyderbad) and his team for the support in developing this method.

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