Asian Journal of Chemistry; Vol. 33, No. 2 (2021), 307-313

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.22984

Identification of Tartaric Acid Adduct Impurities in Dipyridamole Capsule Formulation Related Substances Method

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Received: 5 September 2020; *Accepted*: 22 October 2020; *Published online*: 15 January 2021; AJC-20213

Two tartaric acid adduct degradation products namely dipyridamole tartaric acid monoester and dipyridamole ditartaric acid ester are observed in a dipyridamole capsule formulation. The adduct impurities are inevitable in the formulation due to the interaction of multi-layers of dipyridamole on tartaric acid pellets. Present study reported a simple procedure for generating these two major adducts degradation products from a mixture of dipyridamole drug substance and tartaric acid by stress study. The obtained stress mixture was characterized by liquid chromatography-tandem mass spectrometry (LC-MS) to assure the identity of adduct degradant impurities. The obtained solid stress mixture was stable for more than one year and the prepared solution can be used as reference solution to identify both the degradants during related substance analysis. Practically, the identification of tartaric acid degradants applied to the British pharmacopeia monograph related substances method, where no mechanism for identification of these adduct impurities was described. This study establishes relative retention times for the British pharmacopeia method, which enables the chemist to monitor these two major degradants during quality control release testing and shelf life stability. The same kind of experimental approach for identifying tartaric acid adduct impurities in the British pharmacopeia method can be extended to any of the in-house laboratory-developed related substance methods.

Keywords: Dipyridamole, Degradation, Related substances, Adduct impurities, Chromatographic purity.

INTRODUCTION

Dipyridamole is an adenosine reuptake inhibitor and a phosphodiesterase inhibitor with antiplatelet and vasodilating activity. As a result, the compound is therefore used in thromboembolic disorders [1]. Early clinical trials questioned the efficacy of dipyridamole alone or in combination with aspirin, probably due to its variability in bioavailability. A modified extended release formulation of dipyridamole available in the market with improved bioavailability [2]. However, the physical and biochemical properties of dipyridamole would seem to be completely unsuitable for the typical development of a modified release form. The biological half-life of dipyridamole is relatively short, existing levels in the blood reportedly drop quickly and a uniform dipyridamole level in the blood can be obtained only if the active substance is resorbed continuously [3].

Dipyridamole is reportedly only soluble in an aqueous medium in the acid range and above a pH of 4, the substance is practically insoluble in water. Thus, the dipyridamole can be dissolved and diffused outwards tartaric acid pellets to resorb the dipyridamole in intestinal juices having a pH of 6 to 7. The tartaric acid pellets used in the formulations of the modified release is hydrophilic and capable of maintaining a pH where the dipyridamole is soluble. But during the shelf-life stability, this tartaric acid in pellets interacts with dipyridamole, which can lead to esterification. The esterification of tartaric acid with the hydroxyl groups of dipyridamole leads to major degradants monoester impurity (dipyridamole tartaric acid monoester) and diester impurity (dipyridamole ditartaric acid ester) (Fig. 1).

Literature survey revealed that some analytical methods are available for the determination of dipyridamole from the biological matrices [4-6] and few methods are reported for the determination of dipyridamole in pharmaceutical preparation [7-11]. Few methods reporting dipyridamole impurity analysis have been described in the literature [12-14] and pharmacopeia

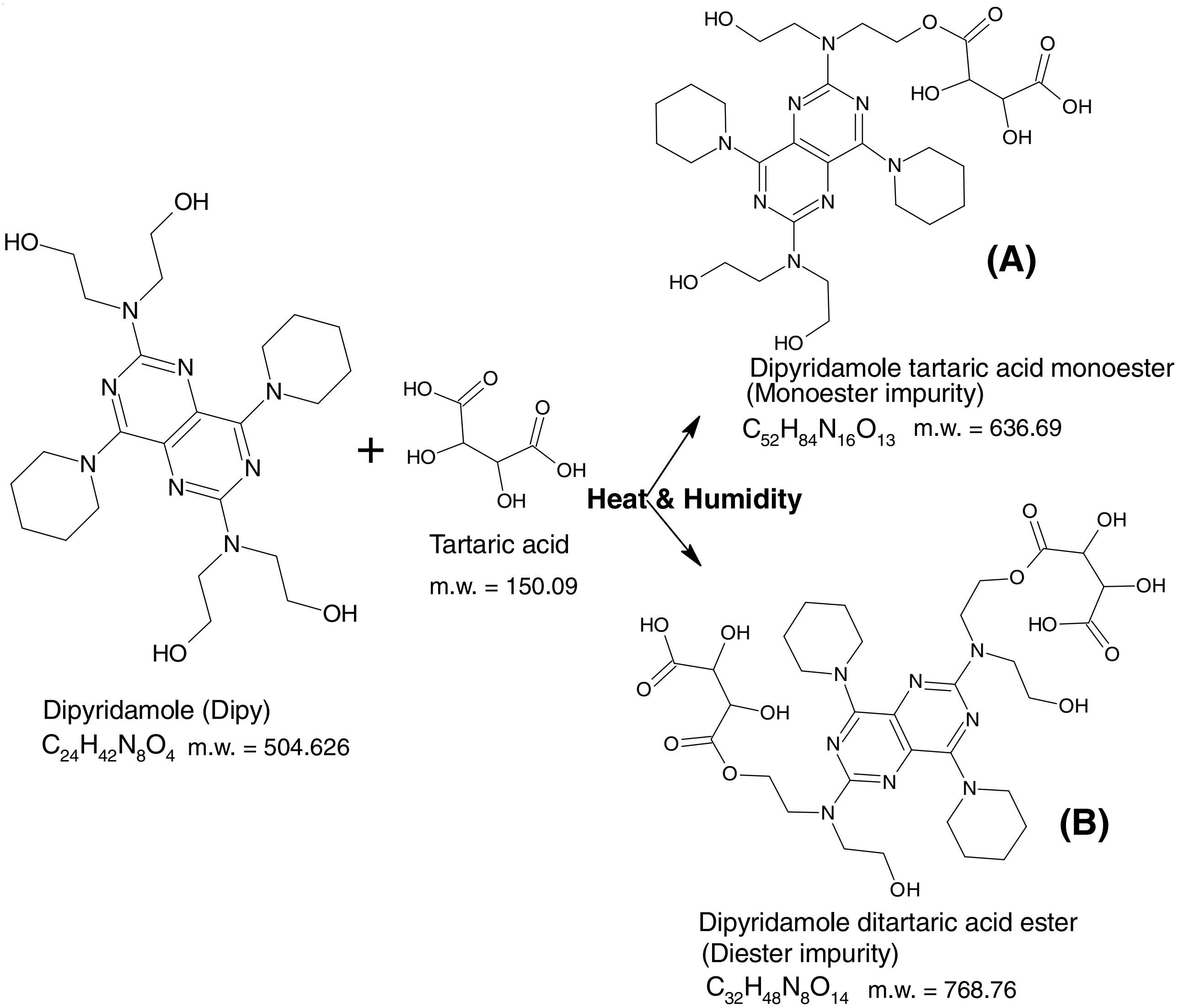

Fig. 1. Schematic diagram showing the interaction of dipyridamole and tartaric acid and the formation of degradants (a) monoester impurity and (b) diester impurity

[15-17]. Some reports [13,14] regarding the impurity methods for capsule formulations did not mentioned the presence of diester impurity. Only the British pharmacopeia monograph for dipyridamole prolonged-release capsules [17] related substances method (BP-RS) mentioned two major ester degradant impurities having a limit of 4% for monoester impurity and 1% for diester impurity. But their relative retention times or any way of identification of impurities was not mentioned in the British pharmacopeia monograph or any of all available literature. There is no monograph for capsule formulation in European pharmacopeia, but the existing drug substance monograph of European pharmacopeia [16] related substances chromatographic conditions are the same as in the British pharmacopeia capsules formulation monograph [17].

The control of drug chemical impurities is currently a critical issue for the pharmaceutical industry. The presence of unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Usually, the identification of impurities in chromatography will be made by injecting its reference standards supplied by different compendia. In India, nowadays, the purchase of reference standards of pharmaceutical substance impurities is restrictive, because only a few pharmacopeias, such as the United States or the European offer these substances at high prices and in a small amount. Standards for tartaric acid ester impurities are not yet available from these compendia or other known sources. Therefore, there is a need for developing an alternate procedure to identify these impurities not only in published British pharmacopeia method but also in any of the in-house developed related substance methods. The similar kind of alternative procedure to identify impurity in related substances method, rather than injecting impurity standard solution, was mentioned in some of United States pharmacopeia monographs [18-21]. There is a need for technical specifications establishment for these two ester impurities in method, to assure the user of the generic drug product of their identity, strength, quality and purity. The main objective of this study is to develop a procedure to identify these tartaric ester impurities in the BP-RS method [17], which was not specified in the monograph and predicting their quantification factors without even any need for physical quantities. The procedure involves the generation of tartaric acid ester impurities by humidity stress and assuring their identity by LC-MS method and establishing relative retention times in the BP-RS method. The produced humidity stress solid mixture shall be used to prepare identification solution during every finished product and stability analysis of capsule formulation to identify tartaric acid ester impurities.

EXPERIMENTAL

Dipyridamole (> 98% purity) and tartaric acid (> 99%) obtained from Sigma-Aldrich, USA. Dipyridamole standard and reference peak identification solution (for identifying impurities A, B, C, D, E & F) were obtained from European pharmacopeia reference standards. Commercially available aspirin and dipyridamole (extended-release) capsules 25 mg/ 200 mg strength under trade name Aggrenox marketed by Boehringer Ingelheim were purchased at a local drug store. ACS grade potassium dihydrogen phosphate, ammonium acetate, sodium hydroxide, ammonium hydroxide and HPLC grade methanol were purchased from Merck, Germany.

HPLC: The system used for the study was Agilent HPLC 1200 series (Agilent Technologies, Germany) with Ezchrom elite software equipped with G1322A degasser, G1311A quaternary pump, G1315C auto-injector, G16A column oven and G1315C DAD detector.

LC-UV-MS: The mass spectrometry (MS) system used was an Applied BiosystemsSciex API 4000 model (Zug, Switzerland) coupled with the HPLC system consisting of an LC-20AD binary gradient pump, SPD-10AVP UV detector, SIL-10HTC autosampler and a column oven CTO-10ASVP (Shimadzu Corporation, Kyoto, Japan). Data acquisition and processing conducted using Analyst 1.5.1 software.

Generation of tartaric acid ester impurities: For the current study, a solid mixture of tartaric acid and dipyridamole was prepared by mixing each of 1 g quantity in a petri dish. This (1:1) solid mixture was subjected for 10 days of humidity stress at 40 ºC/75%RH. The sample solutions were prepared by weighing about 10 mg of dipyridamole equivalent stress solid mixture into a 10 mL flask, dissolved in 60% methanol by sonication to get 1.0 mg mL^{-1} concentration. Filtered solutions were injected into the chromatograph.

Generation of impurities for quantitative factor evaluation: For quantification factor evaluation, the solid mixture of tartaric acid and dipyridamole stress was made in a volumetric flask to nullify the sampling error from a petri dish. Weighed accurately about 100 mg of tartaric acid and 100 mg of dipyridamole in a 100 mL flask. The solid mixtures were subjected to humidity stress at 40 ºC/75% RH and samples were withdrawn at 5 and 10 days time intervals. The sample solutions were prepared by dissolving in 60% methanol by sonication to get 1.0 mg mL^{-1} of concentration. The solutions were filtered through a 0.45 µm syringe filter before injecting onto the chromatograph. These 5 and 10 days stress prepared solutions were used to predict the quantification factor of major degradants monoester impurity (dipyridamole tartaric acid monoester) and diester impurity (dipyridamole ditartaric acid ester).

Method-1/BP-RS HPLC conditions: In method-1, liquid chromatographic conditions were the same as in the British pharmacopeia monograph for dipyridamole prolonged-release capsules [17] related substances (BP-RS) test. The column used was Zorbax Eclipse plus 100 × 4.6 mm, 3.5 µm (Agilent make). The mobile phase-A, 7.5 mM potassium dihydrogen phosphate (pH 7.0) and mobile phase-B as methanol was used. The flow rate was 1.2 mL/min. The gradient program was: 0.01 min-60% B, 19.0 min-95% B, 24.0 min-60% B and 29.0 min-60% B. The detection was carried out at a wavelength of 295 nm. The injection volume was 5 µL. The column compartment temperature was maintained at 45 ºC and the sample compartment temperature was maintained at 25 ºC. All chromatographic conditions of method-1 along with method-2 are presented in Table-1. All the calculations concerning the quantitative analysis were performed with external standardization by measurement of peak areas.

Method-2/LC-MS conditions: There is a need to assure the identity of tartaric acid ester impurities in stress samples by LC-MS. The chromatographic conditions were the same as described earlier; the only changes were, one is slowed down the gradient for better separation and the other is mobile phase-A as pH 7.0, 10 mM ammonium acetate buffer to make it compatible to mass spectrometric analysis. The gradient program was: 0.01 min-55% B, 5.0 min-55% B, 30.0 min-95% B, 33.0 min-55% B and 38.0 min-55% B. The humidity stress sample solution was injected into the LC-MS system. Molecular ions

TABLE-1
CHROMATOGRAPHIC CONDITIONS COMPILATION

Parameter	Method-1/BP-RS[a] chromatographic conditions	Method-2/LC-MS analysis chromatographic conditions
Column	Zorbax Eclipse plus 100 × 4.6 mm, 3.5 µm	Zorbax Eclipse plus 100 × 4.6 mm, 3.5 µm
Mobile phases	Mobile phase-A: pH 7.0-7.5 mM potassium dihydrogen phosphate buffer; Mobile phase-B: Methanol	Mobile phase-A: pH 7.0-10 mM ammonium acetate buffer; Mobile phase-B: Methanol
Gradient program	0.01 min-60% B, 19.0 min-95% B, 24.0 min-60% B and 29.0 min-60% B	0.01 min-55% B, 5.0 min-55% B, 30.0 min-95% B, 33.0 min-55% B and 38.0 min-55% B
Runtime	29 min	38 min
Flow rate	1.2 mL/min	1.2 mL/min
Injection volume	5 µL	5 µL
Column temperature	45 °C	45 °C
Detector	U.V. detector-295nm.	U.V. detector at 295nm and Mass detector

[a]As in British pharmacopeia monograph for dipyridamole prolonged-release capsules [Ref. 17] related substances method.

of both the impurities characterized by obtaining the mass spectra on an AB Sciex API 3000 ES/MS. The sample was introduced into the source through a turbo ion spray interface in positive and negative ionization in scan mode. The nebulizer and curtain gases used were zero air and nitrogen, respectively. The ion source voltage was maintained at 4200V. Focussing potential and declustering potential were kept at 300 and 50V, respectively. All the parameters of LC and MS were controlled by Analyst software version 1.5.1.

RESULTS AND DISCUSSION

The main objective of this study is to generate the tartaric ester impurities of dipyridamole, assuring their identity by LC-MS and developing a procedure to identify their retention times in the BP-RS method. The established relative retention times (RRT's) with respect to dipyridamole in BP-RS method were used in the monitoring of these adduct degradants during the routine analysis of formulation samples.

Analysis of stress solid mixture by LC-MS: Prepared solutions were injected into method-2/LC-MS conditions, but initially, the solutions were examined in a UV detector to obtain the elution pattern of dipyridamole and degradants, then systematically programmed to allow them into mass spectrometry. The typical chromatogram of UV detector in LC-MS conditions is shown in Fig. 2. From the UV chromatogram of stress solid mixture (Fig. 2a), it is evident that there were some unknown degradant peaks along with dipyridamole. The dipyridamole elutes at about 15.2 min. The % area of dipyridamole is about 46%, a major peak at RT 2.2 min is about 6.5% (unknown-1), another major peak at RT 7.7 min is about 44.5% (unknown-2), the sum of all other unknown degradants are less than 3% and out of these all other unknowns, no individual exceeded more than 1%. Anticipating these two major unknowns at RT 2.2 min and RT 7.7 min were to be related to tartaric acid ester impurities, attempts were made to evaluate these unknown impurity mass numbers by connecting to a mass spectrometer. The mass detector was programmed to allow these major unknowns and partially allow the main dipyridamole peak to avoid contamination of the ion source. The mass spectrums for major unknowns at RT 2.2 min and RT 7.7 min are presented in Fig. 3. The mass numbers in positive ionization mode and negative ionization mode for unknowns and dipyridamole are tabulated in Table-2.

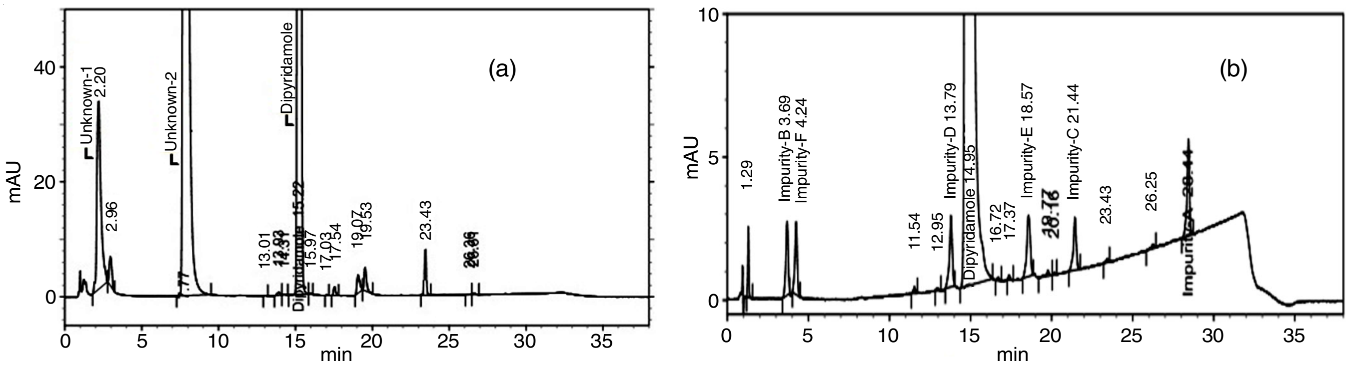

Fig. 2. Typical UV detector chromatograms of method-2/LC-MS conditions (a) (1:1) solid mixture of tartaric acid and dipyridamole stress at 40 °C/75% RH for 10 days (b) Ph. Eur. Dipyridamole reference peak identification solution

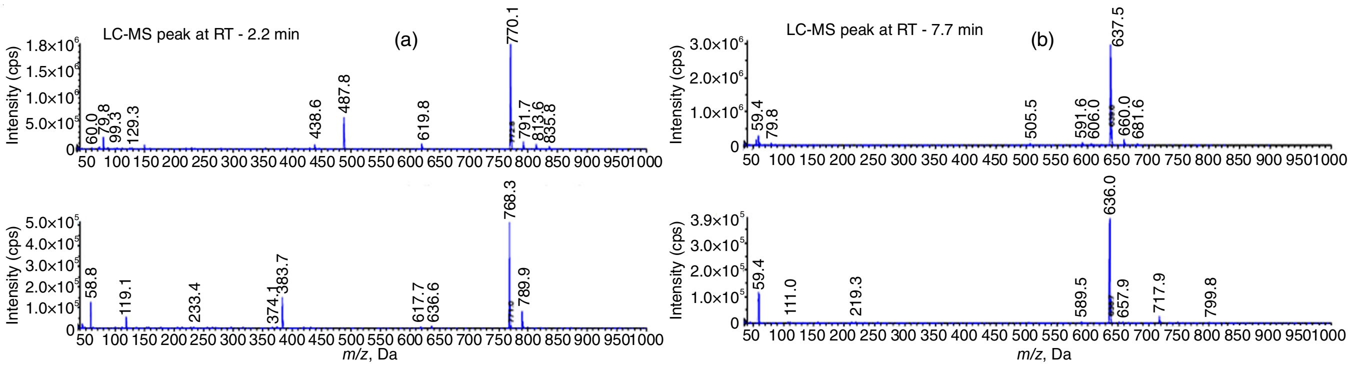

Fig. 3. LC-MS analysis in positive and negative ion modes (a) mass spectrum of Unknown-1 at RT 2.2 min (b) mass spectrum of unknown-2 at RT 7.7 min

TABLE-2
METHOD-2 MASS NUMBERS OF UNKNOWNS ALONG WITH DIPYRIDAMOLE IN POSITIVE AND NEGATIVE IONIZATION MODE

Name of the peak	Mass number (M+H)	Mass number (M-H)	Theoretical mass number
Dipyridamole (15.2 min)	505.5	503.7	504.60
RT-2.2 min Unknown-1 (diester impurity)	770.1	768.3	768.76
RT-7.7 min Unknown-2 (monoester impurity)	637.5	636.0	636.69

Interpretation of mass spectrum for unknown-1: In the positive mode, ESI-MS analysis of the unknown-1 exhibited a protonated molecular ion peak *m/z* 770. The difference of mass between impurity and dipyridamole is 264 amu, indicating deletion and addition on dipyridamole. During the esterification of two molecules of tartaric acid with two hydroxyl groups of dipyridamole, the loss of two water molecules leads to the *m/z* 770. The negative mode ESI-MS analysis of the unknown-1 exhibited molecular ion *m/z* 768, clearly concluded that the labeled unknown-1 eluting at RT 2.2 min in LC-MS method is dipyridamole ditartaric ester impurity.

Interpretation of mass spectrum for unknown-2: In the positive mode, ESI-MS analysis of the unknown-2 exhibited a protonated molecular ion peak *m/z* 638. The difference of mass between impurity and dipyridamole is 132 amu, indicating deletion and addition on dipyridamole. During the esterification of tartaric acid with one hydroxyl group of dipyridamole, there is a loss of water molecule leading to the *m/z* 638. The negative mode ESI-MS analysis of unknown-2 exhibited molecular ion *m/z* 636, clearly concluded that the labeled unknown-2 eluting at RT 7.7 min in LC-MS method is dipyridamole mono ester impurity.

Identification of dipyridamole tartaric ester impurities in method-1/BP-RS method: Unknowns 1 & 2 were evaluated and their identity was assured by mass spectrometry as dipyridamole diester and monoester impurities, respectively. The final objective was to identify these ester impurities elution in the BP-RS method and establishing relative retention times. For this, two parallel analyses were performed on HPLC-1 equipped with a method-1/BP-RS method, and another HPLC-2 equipped with method-2/ LC-MS conditions, but now the HPLC-2 was connected to only UV detector, not for mass spectrometry. Stress solution was injected into HPLC-2 and collected the RT 2.2 min and 7.7 min peaks into separate labeled vials from HPLC vent from multiple injections to make at least 1 mL volume. The RT 2.2 min corresponds to diester impurity and RT 7.7 min corresponds to monoester impurity. These solutions of RT 2.2 min and RT 7.7 min were separately injected into HPLC-1 equipped with BP-RS conditions along with dipyridamole peak identification EPCRS. The BP-RS chromatograms are presented in Fig. 4. The RT 2.2 min collected solution eluted at RT 0.73 min and the RT 7.7 min collected solution was eluted at RT 1.85 min in BP-RS conditions, the related chromatograms are presented in Fig. 5. The relative retention time of particular impurity is the ratio of impurity retention time and dipyridamole retention time. The relative retention times against dipyridamole were calculated as dipyridamole diester as RRT 0.09 min and dipyridamole mono ester impurity as RRT 0.23 min. The objective of finding the elution and calculation of relative retention time of ester impurities was achieved. The retention times and relative retention times of tartaric acid ester impurities along with other European pharmacopeia impurities in the BP-RS method are presented in Table-3.

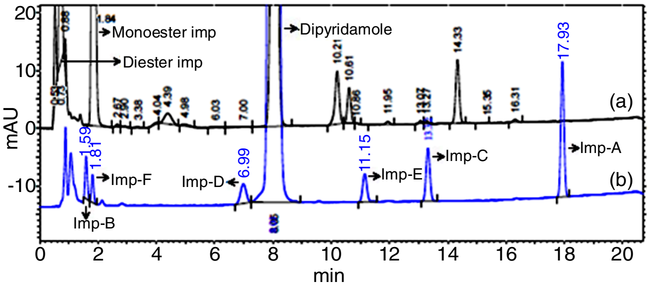

Fig. 4. Typical chromatograms of method-1/BP-RS conditions (a) (1:1) Solid mixture of tartaric acid and dipyridamole stress at 40 °C/ 75% RH for 10 days (b) Ph. Eur. Dipyridamole reference peak identification solution

Prediction of relative response factor for ester impurities: When impurities to be determined with greater certainty at a given wavelength of UV detector, using impurity itself as standard is helpful or an alternative approach was used by applying a relative response factor based on the response of the impurity relative to its active drug component. For the prediction of the relative response factor for ester impurities, a novel approach was used based on the mass balance of dipyridamole in the stress sample. The proposed kind of procedure had greater accuracy when the degradation was limited to majorly one or two degradants from an active drug component. For calculating the impurity levels, the relative response factor of respective impurities was applied to normalize the response of impurities against dipyridamole. The relative response of an impurity higher than the value of 'one' means, the impurity shows more

TABLE-3
ELUTION OF IMPURITIES IN BP-RS AND IN-HOUSE LC-MS METHOD CONDITIONS

Name	Method-1/BP-RS method conditions retention time & RRT's	Method-2/Inhouse LC-MS method conditions retention time & RRT's
Dipyridamole	7.89 min (RRT 1.00)	14.95 min (RRT 1.00)
EP Impurity-A	17.87 min (RRT 2.26)	28.44 min (RRT 1.90)
EP Impurity-B	1.61 min (RRT 0.20)	3.69 min (RRT 0.25)
EP Impurity-C	13.23 min (RRT 1.68)	21.44 min (RRT 1.43)
EP Impurity-D	6.85 min (RRT 0.87)	13.79 min (RRT 0.92)
EP Impurity-E	11.06 min (RRT 1.40)	18.57 min (RRT 1.24)
EP Impurity-F	1.81 min (RRT 0.23)	4.24 min (RRT 0.28)
Monoester impurity	1.84 min (RRT 0.23)	7.77 min (RRT 0.52)
Diester impurity	0.73 min (RRT 0.09)	2.20 min (RRT 0.15)

BP-RS: British Pharmacopeia monograph for dipyridamole prolonged-release capsules [Ref. 17] related substances method; EP: European Pharmacopeia; RRT: Relative retention time calculated against dipyridamole retention time.

Note: BP-RS and E.P. chromatographic conditions were similar [16,17] and the peak identification solution having Impurity-A, B, C, D, E and F is available from Ph.Eur hence the naming given as EP.

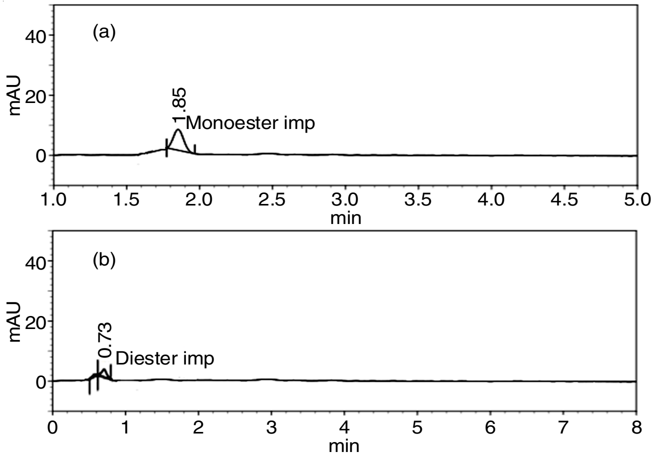

Fig. 5. Method-1/BP-RS conditions chromatograms representing (a) elution of method-2 RT 7.7 min collected solution corresponds to monoester impurity (b) elution of method-2 RT 2.2 min collected solution corresponds to diester impurity

response compared to its main component at a given wavelength and *vice-versa*. When an impurity having a relative response factor higher than the value one, then it exhibits a more % area in a chromatogram due to its higher response than the actual mass balance. That means the main drug component % area gets lower than its real mass balance. Based on the changes in the mass balance of drug component with its % area in a degraded sample, the relative response factor of impurity can be predicted. This kind of approach can be applied to the dipyridamole stress sample, where the two major degradants formation is dominant. Both the ester impurity structures differ only by the number of tartaric acid groups attached to dipyridamole; hence the assumption is that there is no considerable difference in their absorptivity at a given wavelength 295 nm. For the 10 days stress sample, the % total degradation observed by %area from chromatogram is about 54%, which means the dipyridamole %area is about 46%. This 10 days stressed sample mass balance of dipyridamole calculated against the external dipyridamole standard and the observed content was 51%. Dipyridamole %area as 46% was less than the computed content 51%, indicating the response contribution from impurities was high. Indirectly, the ratio of % actual content and %area of dipyridamole corresponds to the combined relative response of impurities in the stress sample. The % total of minor degradants in chromatogram by %area, other than ester impurities is only < 3%; hence there is an insignificant contribution with the minor degradants during the prediction of these major ester impurities relative response factor. Thus, the formulae 2 and 3 can be applied to predict the relative response factor for ester impurities with a calculated error of less than 6%. The prediction of the relative response factor gives a significant assurance for finding the purity of active substance in a formulation sample. The relative response factor of ester impurities prediction is given in Table-4. According to the US pharmacopeia general chapter <621>, the quantification factor 1.0 shall be used if the impurities are having a response factor ranging from 0.8 to 1.2. Considering all errors, the predicted relative response is lying in the range of 1.0 to 1.2; hence the usage of 1.0 quantification factor for both the ester impurities is appropriate and acceptable.

$$\text{Relative response factor} = \frac{R_i}{R_S} \times \frac{C_S}{C_i} \tag{1}$$

where, R_i = peak response of impurity, R_S = peak response of active component solution, C_S = concentration of active componenet solution (μg/mL), C_i = concentration of impurity solution (μg/mL).

$$\text{Relative response factor of impurity by mass balance} = \frac{A}{B} \tag{2}$$

A = % content of dipyridamole in stress sample against an external dipyridamole standard; B = % Area of dipyridamole from stress sample chromatogram.

$$\text{Error (\%)} = \left(\frac{A}{B}\right) - \left(\frac{A}{B+C}\right) \times \left(\frac{1}{A/B}\right) \times 100 \tag{3}$$

A = % content of dipyridamole in stress sample against external standard; B= % area of dipyridamole from stress sample chromatogram; C= % of all known and unknown other than two major ester impurities.

Analysis of formulated samples: The formulated samples of a fixed dose combination of aspirin and dipyridamole capsules 25/200 mg strength 1 month 40 ºC/75% RH were analyzed for determination of impurities along with ester impurities. Each sample preparation was preceded by taking dipyridamole pellets equivalent to 20 mg of dipyridamole to the 20 mL amber colour flask to make the concentration of dipyridamole 1 mg mL^{-1}. Diluent (15 mL) was added and sonicated for 10 min with intermittent shaking, then it was made up to the volume. Filtered samples were injected into HPLC with chromatographic conditions. Before running the samples into HPLC, system suitability was tested by injecting diluent as blank, peak identification solution supplied by European pharmacopeia and 5 replicate injections of dipyridamole standard having 2 μg mL^{-1}. The typical chromatogram of the formulation sample is given in Fig. 6. The impurities were calculated by using the formula

TABLE-4
RELATIVE RESPONSE FACTOR EVALUATION FOR ESTER IMPURITIES

Sample name	% Assay[a] of Dipy (A)	% Area[b] of Dipy (B)	% Area of all impurities (100-B)	% Area of unknowns other than ester degradants (C)	RRF[c] = (A/B)	%Error
(1:1 w/w) Tartariac acid: Dipyridamole 10 days 40 °C/75% RH	51	46	54	2.9	1.108	5.8
(1:1 w/w) Tartariac acid: Dipyridamole 5 days 40 °C/75% RH	68	62	38	1.6	1.096	2.4

[a]% Assay = Content of dipyridamole against an external standard; [b]% Area = % Area of dipyridamole from stress chromatogram; [c]RRF = Relative response of ester impurities. Dipy = Dipyridamole

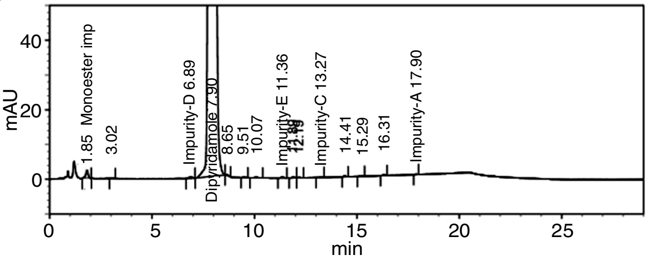

Fig. 6. Typical chromatogram of BP-RS conditions for capsule formulation one month stress at 40 °C/75% RH

mentioned below by applying the relative response factors of impurities. There is no difference in impurity results observed between BP-RS and LC-MS compatible method, proving their equivalency. In the BP-RS method, the monoester impurity having interference from EP-impurity-F and can be noticed from Fig. 4. But EP-impurity-F is claimed as unspecified in pharmacopeia and controlled in drug substance; hence there is no discrepancy in the quantification of monoester impurity was noticed in the formulation. The present work limited to only the BP-RS method, not validating the LC-MS conditions for the UV detector, where the monoester and impurity-F were well separated.

$$\text{Impurity }(\%) = \left(\frac{R_U}{R_S}\right) \times \left(\frac{C_S}{C_U}\right) \times \left(\frac{1}{F}\right) \times 100 \qquad (4)$$

where, R_U = peak response of each impurity from the sample solution; R_S = peak response of dipyridamole from the standard solution; C_S = concentration of dipyridamole in the standard solution (mg/mL); C_U = nominal concentration of dipyridamole in the Sample solution (mg/mL); F = relative response factor of impurity

Conclusion

In this study, two tartaric ester impurities named as monoester impurity and diester impurity were identified in the British pharmacopeia related substances method and their quantification factors were predicted and successfully applied for the analysis of the formulation sample. The ester impurities formation in stress solid mixture was assured by LC-MS analysis. The stress solid mixture was stable for more than one year and the integrity of ester degradant peaks maintained throughout the period; hence its freshly prepared solution can be used as a suitability solution to identify ester impurities during quality control and shelf life stability testing. In the same way, the approach for identifying dipyridamole monoester and diester adduct degradants in British pharmacopeia related substances method can be extended to any of the in-house laboratory-developed related substance methods.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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