Comparative Study of Forced Degradation Behavior of Telmisartan by UPLC and HPLC and Development of Validated Stability Indicating Assay Method According to ICH Guidelines

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Abstract

A novel comparative force degradation ultra-performance liquid chromatographic method was developed and validated for Telmisartan and its degradation products. Telmisartan was subjected to acid (0.1 M HCl), neutral (water) and alkaline (0.1 M NaOH) hydrolytic conditions at 80°C, as well as to oxidative decomposition (H₂O₂) at room temperature. Photolytic studies were carried out by exposing this drug into sunlight (60,000-70,000 lux) for 2 days. Additionally, the solid drug was subjected to 50°C for 60 days in a hot air oven for thermal degradation. The UPLC chromatographic separation was performed on Acquity UPLC BEH C18 column (1.7 μm, 2.1 mm × 150 mm) using isocratic mode (ACN:water, 70:30 v/v) at flow rate of 0.2 ml min⁻¹ and HPLC chromatographic separation was achieved on phenomenex C18 using isocratic mode (ACN:10 mM ammonium acetate, pH 4.5, 85:15 v/v) at flow rate of 1.0 ml min⁻¹. Telmisartan was found to degrade significantly in acid, base and oxidation, the drug was found to be stable in neutral, thermal and photolytic stress conditions. The ultra performance liquid chromatography (UPLC) and high performance liquid chromatography (HPLC) area %RSD were calculated to be 0.0039 and 0.0015 respectively. The UPLC and HPLC linearity of the proposed method were investigated in the range of 10-50 μg mL⁻¹ and 30-150 μg mL⁻¹. The r² value of UPLC and HPLC were found to be 0.9987 and 0.9989 respectively. Method detection limit (MDL) and Method quantification limit (MQL) were found to be 0.250 μg mL⁻¹ and 1.20 μg mL⁻¹ respectively for HPLC. The %R.S.D. values for intra-day and inter-day precision were <1.0%, confirming that the method was sufficiently precise. The validation studies were carried out fulfilling ICH requirements. The developed method was simple, fast, accurate and precise and hence could be applied for routine quality control analysis of Telmisartan in solid dosage forms.

Keywords: Telmisartan; Stress testing; Stability indicating assay; Validation; UPLC; HPLC

Introduction

The International Conference on Harmonization (ICH) drug stability test guideline Q1A (R2) requires that analysis of stability samples should be done through the use of validated stability-indicating analytical methods. It also recommends carrying out stress testing on this drug substance to establish its inherent stability characteristics and to support the suitability of the proposed analytical procedure [1-7]. The objective of reducing analysis time and maintaining good efficiency, has been substantial focus on high-speed chromatographic separations. Recently, commercially available an innovative ultra performance liquid chromatography (UPLC) has proven to be one of the most promising developments in the area of fast chromatographic separations. In this work comparative reverse phase chromatographic stability indicating assay method was developed using UPLC and HPLC for Telmisartan bulk drug. Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects. The chemical name is 2-(4-[(4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H,1,3-benzodiazol-1-yl]methyl]phenyl) benzoic acid (Figure 1) [8-9].

In order to enhance chromatographic performances in terms of efficiency and rapidity, LC has recently evolved in the development of short columns packed with small particles (sub-2 μm) working at...
high pressures (>400 bar). Advantages of small particles working at high pressure will be discussed in terms of sensitivity, efficiency, resolution, and analysis time. Potential problems encountered with high pressure in terms of frictional heating and solvent compressibility will also be discussed even if systems working at a maximum pressure of 1000 bar are not influenced by these parameters and give reliable and reproducible results. According to the chromatographic performances afforded by small particles, the latter can be used for two main objectives. First, small particles can be used to perform fast and ultra-fast analyses since a good efficiency can be maintained with short columns and at high flow rate. Second, high resolution can be generated with longer columns, close to the optimal flow-rate. As reported for monoliths, high efficiency is needed in several domains (proteomics and metabolomics) [10-13].

In the literature, a few methods have been reported for the estimation of Telmisartan by spectrophotometric methods [14], HPLC [15,16], LC-MS/MS [17,18]. The major objective of the present work is to develop stress degradation studies of Telmisartan under different ICH recommended stress conditions, and to establish a validated stability-indicating UPLC/HPLC method for reducing analysis time and solvents. So far to our knowledge there was no method reported for comparative UPLC/HPLC method yet, on the development of stability-indicating assay method for this drug.

**Experimental**

**Chemicals**

Telmisartan was obtained as a gratis sample from jubilant organosys (Noida, India). Analytical reagent (AR) Sodium hydroxide and hydrogen peroxide were purchased from S.D. Fine-chem. Hydrochloric acid and acetonitrile (99.6%) was from Merck India (Mumbai). All other chemicals were of analytical grade.

**Instrumentation**

**Ultra performance liquid chromatography:** UPLC was performed using a Waters Acquity System equipped with binary solvent delivery pump, an auto sampler and PDA detector. The chromatographic separation was performed using a Waters Acquity BEH 150×2.1 mm, 1.7 μm, C18 column. The mobile phase containing a mixture of acetonitrile and water in the ratio of 70:30 (v/v) at a flow rate of 0.2 mL min⁻¹ was used. The injection volume was 2 μL; mobile phase was used as a diluent while the column was maintained at 30°C. Forced degradation studies were carried out with a photo diode array detector.

**High performance liquid chromatography:** The HPLC system used for chromatographic development was shimadzu, separation module with a PDA detector. HPLC system (Shimadzu, Japan) consisted of a LC-10AT VP pump, a SPD-10AVP, PDA detector, a phenomenex C18 (250mm×4.6mm, 5 μm) column, a Phenomenex, HPLC guard cartridge system and a Class LC10/M10A software. Mobile phase consisting of acetonitrile and buffer (10mM ammonium acetate, pH 4.5) in the ratio 80:20 (v/v) in an isocratic mode with the flow rate of 1.0 mL min⁻¹ was employed at ambient temperature. The injection volume was 20 μL while detector was set at 230 nm.

**Others:** pH of the mobile phase was checked on microprocessor water proof water tester (pH tester 20, eutech instruments, oaktion, USA). The overall illumination at the point of placement of samples was 6000 lux, which was tested using a calibrated lux meter (Lutron LX-102 digital light meter, Marcucci S.P.A, vignate, Milan). Thermal stability study was performed in a hot air oven (Oven universal with thermotext thermostat TIC-4000N, S.M. Industries, New Delhi, India).

**Degradation studies**

Stress studies were performed under conditions of dry heat (thermal studies), hydrolysis (acidic, alkaline and neutral), oxidation, and photolysis, as mentioned in ICH Q1A (R2) [1-4]. The approach suggested by Singh and Bakshi was adopted for these studies. A minimum of four samples were generated for every stress condition, viz., blank solution stored under normal conditions, the blank subjected to stress in the same manner as this drug (Telmisartan), a zero time sample containing this drug (which was stored under normal conditions), and this drug solution subjected to stress treatment. Hydrolytic decomposition of Telmisartan was conducted at 80°C in 0.1 M HCl, water, and 0.1 M NaOH at a drug concentration of 2 mg mL⁻¹ until sufficient degradation (~20% of initial amount) of this drug was achieved. For oxidative stress studies, Telmisartan was dissolved at a concentration of 3 mg mL⁻¹ in 30% H₂O₂ and kept for two days at room temperature. Photolytic studies of the dry drug and this drug in solution in acetonitrile at a concentration of 2 mg mL⁻¹ were performed by exposure to sunlight during the daytime (60,000-70,000 lux) for 2 days.

**Chromatography and development of a stability-indicating method**

UPLC was performed with a binary solvent delivery pump, an auto sampler, and PDA detector of Acuity UPLC system manufactured by Waters Corporation, Milford, Massachusetts, USA; data were acquired and processed using Empower software. An initial literature search revealed that some reported HPLC methods for Telmisartan were developed on either C8 or C18 columns, using different temperature conditions. Peak shapes were not good and there was substantial tailing. So, attempts were made to develop a simple method on an advanced BEH C18 column, with possible lowering of retention time at 30°C column temperature. Separations were achieved using isocratic elution. Before use, the mobile phase was filtered through 0.22 μm PTFE membranes and degassed. The injection volume was 2 μL and the mobile phase flow rate kept constant at 0.2 mL min⁻¹. The detection wavelength was 230 nm; PDA analysis was conducted to study the behaviour at other wavelengths. First, UPLC studies were performed on all reaction solutions individually, and then on a mixture of degraded drug solutions. Different conditions, for example pH, mobile phase composition, and column temperature were varied to obtain good separation between this drug and the degradation products. Methanol was avoided during the study because of its significant absorption at the detection wavelength of this drug between 210 and 215 nm. Acuity UPLC BEH C18 column (1.7 μm, 2.1 mm×150 mm) stainless steel analytical column was used as stationary phase. In order to determine the method is stability indicating, forced degradation studies were conducted on Telmisartan powder. The analysis was carried out by UPLC with a PDA detector at a wavelength of 230.2 μL of each of forced degradation samples were injected at regular intervals.

HPLC chromatographic analysis was performed at ambient temperature on a Phenomenex (C-18) analytical column with a mobile phase composed of buffer (10 mM Amm.Acetate buffer pH 4.5): acetonitrile (70:30, v/v) and was isocratically eluted at a flow rate of 1.0 mL min⁻¹. A small sample volume of 20 μL was used for each sample run, being injected into the HPLC system. The chromatogram was monitored with UV detection at a wavelength of 230 nm.
Validation of the method

The method was validated in accordance with ICH guidelines Q2 (R1). To establish linearity and range, a stock solution containing 1 mg mL⁻¹ drug in acetonitrile was diluted to yield solutions in the concentration range 10⁻⁵ to 50 μg mL⁻¹. The solutions were injected in triplicate using water–acetonitrile as mobile phase and keeping the injection volume constant (2 μL). To assess precision, six injections of five different concentrations (10, 20, 30, 40, and 50 μg mL⁻¹) were made on the same day and intra-day precision was determined as relative standard deviation. These studies were also repeated on different days to determine inter-day precision. Accuracy was evaluated by fortifying a mixture of decomposed reaction solutions with five known concentrations of this drug and recovery of the added drug was evaluated. The specificity of the method for this drug was established by study of the resolution factor of this drug peak from the nearest other peak. Overall selectivity was established by determination of purity for each degradation product peak by use of PDA detector. Robustness was assessed by changing the temperature of column. Method detection limit (MDL) and method quantification limit (MQL) were determined experimentally, by analysis of samples spiked with decreasing concentrations of the analytes. MDL was defined as the smallest amount of an analyte that can be reliably detected or differentiated from the background for a particular matrix (by a specific method). MQL was calculated as the smallest amount of an analyte that can be reliably quantified with a certain degree of reliability within a particular matrix (by a specific method). In chromatography methods, the limits are often set based on the ratio between the analyte signal and the baseline noise (for example, MDL = Height/Noise ratio of 3, MQL = Height/Noise ratio of 10).

Results and Discussion

UPLC and HPLC studies on the stressed solutions

The forced-degradation study shows that Telmisartan degraded under acid, alkali, neutral & oxidative stresses. The specificity and selectivity of the method with the samples under these stresses were demonstrated through the evaluation of R, R, resolution, and purity data for all peaks in the chromatograms. Telmisartan did not degrade under thermal & photolytic stress conditions. In a mixture of stressed sample) (Figure 2). Ultra-performance liquid chromatography (UPLC) is a new category of separation technique (mixture of stressed sample) (Figure 2). Ultra-performance liquid chromatography (UPLC) is a new category of separation technique that utilizes sub-1.7 μ particles for stationary phase. These particles operate at elevated mobile phase linear velocities to affect dramatic increase in resolution, sensitivity and speed of analysis.

Development and optimization of the method

UPLC: Initially, this drug was analyzed on a BEH C18 column (150 mm x 2.1 mm, 1.7 μm particle) using acetonitrile: water (50:50) as mobile phase at a flow rate of 0.2 mL min⁻¹ and a column temperature of 25°C. Under these conditions, the shape of this drug peak was not good. Subsequent trials were made on stressed samples using different amounts of acetonitrile, pH, and temperature. The peaks for this drug and the degradation products were not well separated or did not have an acceptable shape at column temperatures <30°C and acidic pH. The best separation was achieved on the same column at 30°C using the mobile phase acetonitrile : water (70:30) in an isocratic mode. The flow rate was kept at 0.2 mL min⁻¹ at constant volume 2 μL and the detection wavelength was 230 nm.

UPLC studies on Telmisartan under different stress conditions suggested the following degradation behaviors

Alkaline hydrolysis: This drug Telmisartan gradually degraded with time on heating at 80°C in 0.1 M NaOH after 08 hours, forming degradation products shown in chromatogram. This drug showed susceptible behavior towards alkaline stress and it was observed that around 60% of degradation and the rate of hydrolysis in alkaline were faster as compared to that of acid. In a mixture of stressed samples the degradation products appeared at RP 1.105, 1.465 pertaining to DP II and DP IV.

Acidic condition: It was observed that around 30% of this drug degraded on heating at 80°C in 0.1M HCl for 08 hours. An acidic hydrolysis, one peak of degradation product was observed at RP 1.246 along with this drug peak at RP 1.639, in mixture of stressed samples the degradation products appeared at RP 0.760 pertaining to DP I.

Table 1: Retention times and relative retention times of various peaks with their peak purity data.

| PEAKS | UPLC | HPLC |
|-------|------|------|
|       | Retention Time (R,) | Relative Retention Time (RR,) | Retention Time (R,) | Relative Retention Time (RR,) |
| DP I  | 1.246 | 0.760 | 1.395 | 0.737 |
| Telmisartan | 1.639 | 1.000 | 1.891 | 1.000 |
| DP II | 1.811 | 1.105 | 2.391 | 1.264 |
| DP III | 2.169 | 1.323 | 4.081 | 2.158 |
| DP IV | 2.401 | 1.465 | 5.524 | 2.921 |

RR = Relative retention time
R = Retention time (minutes)

Figure 2: Chromatogram showing separation of Telmisartan and its degradation products in a mixture of stressed samples by a) UPLC & b) HPLC.
Neutral hydrolysis: Neutral hydrolysis was carried out by keeping drug in water at 80°C for 2 days. No degradation was observed.

Oxidative degradation: A degradation product was observed on exposure of this drug to 30% H₂O₂ for 2 days, showing that it was more stable to oxidation than to hydrolytic stress conditions. In mixture of stressed samples, the degradation product appeared at RRₙ 1.323 pertaining to DP III.

Solid-state study: There was no significant degradation of solid Telmisartan on exposure to a dry heat at 50°C for 1 month, which indicates that this drug was stable against thermal stress. After 1 month no extra peak other than this drug was seen.

Photolytic degradation: Drug remains stable even after exposure to direct sunlight for 2 days –~70,000–80,000 lux sun exposures.

HPLC: As UPLC, the same degradation products were appeared in HPLC also.

Alkaline condition: In a mixture of stressed samples the degradation products appeared at RRₙ 1.264(DP II) & 2.921(DP IV).

Acidic hydrolysis: In a mixture of stressed samples the degradation product appeared at RRₙ 0.737 (DP I).

Neutral hydrolysis: No additional peak was found, showing stable behavior in water.

Oxidative degradation: In a mixture of stressed samples the degradation product appeared at RRₙ 2.158 (DP III).

Solid-state study: No degradation was observed showing that it was stable against thermal stress.

| UPLC | Concentration (µg mL⁻¹) | AUC ± S.D., R.S.D. (%) | Concentration (µg mL⁻¹) | AUC ± S.D., R.S.D. (%) |
|------|-------------------------|-----------------------|-------------------------|-----------------------|
| 10   | 43166.00                | 51.316                | 0.119                   | 30                    | 1875036.0              | 17317.9                 | 0.924                  |
| 20   | 87910.330              | 85.440                | 0.097                   | 60                    | 3571026.0              | 11549.3                 | 0.323                  |
| 30   | 123769.98             | 952.321               | 0.479                   | 90                    | 5458671.7              | 577.4                   | 0.106                  |
| 40   | 168638.00              | 555.698               | 0.330                   | 120                   | 7159944.7              | 3462.2                  | 0.484                  |
| 50   | 209296.99              | 601.775               | 0.288                   | 150                   | 9059944.7              | 3462.2                  | 0.382                  |
| 60   | 43166.00               | 51.316                | 0.119                   | 180                   | 1875036.0              | 17317.9                 | 0.924                  |

S.D. = Standard deviation  
R.S.D. = Relative standard deviation  
AUC = Area under curve  

| HPLC | Concentration (µg mL⁻¹) | AUC ± S.D., R.S.D. (%) | Concentration (µg mL⁻¹) | AUC ± S.D., R.S.D. (%) |
|------|------------------------|-----------------------|-------------------------|-----------------------|
| 30   | 30.101                 | 0.096                 | 0.319                   | 30.138                | 0.046                  | 0.153                  |
| 60   | 59.940                 | 0.217                 | 0.362                   | 60.011                | 0.273                  | 0.455                  |
| 90   | 89.907                 | 0.273                 | 0.303                   | 89.955                | 0.308                  | 0.342                  |
| 120  | 120.143                | 0.169                 | 0.141                   | 120.350               | 0.263                  | 0.218                  |
| 150  | 150.448                | 0.508                 | 0.338                   | 150.596               | 0.354                  | 0.235                  |

S.D. = Standard deviation  
R.S.D. = Relative standard deviation  

Table 2: Data for Telmisartan from linearity studies (n=6).

Photolytic degradation: There was no degradation products found in photolytic study.

Validation of developed stability-indicating method: The response for this drug was strictly linear in the concentration range between 10 and 60 µg mL⁻¹. The linearity study data are given in Table 2.

Regression equation

Y=4129X+2659  (UPLC r²=0.999, intercept= 2659)  
Y=59862X+37304  (HPLC r²=0.999, intercept=37304)

Y=AUC, X=conc. in µg mL⁻¹

The data obtained from precision experiments are given in Table 3 for intra and inter day precision studies. The %R.S.D. values for intra-day precision study and for inter-day study were <1.0% confirming that the method was sufficiently precise. Excellent recoveries were made at each added concentration shown in Table 4. Figure 2 shows that the method was sufficiently specific to this drug. The USP resolution factor for this drug peak was >2 from the nearest resolving peak. The method was found to be robust by varying the temperature of column as shown in Table 5. Good separations were always achieved, indicating that the method remained selective for all components under the tested conditions as shown in Figure 2. The influence of retention time for different degradation products (UPLC/HPLC) has been depicted in Figure 3.

The MDL and MQL were found to be 0.250 µg mL⁻¹ and 1.20 µg mL⁻¹ for UPLC and 0.600 µg/ml and 1.900 µg/ml respectively for HPLC.

Table 3: Data of intra-day and inter-day precision studies (n=4).
Comparison study of chromatographic performance

A comparative data on chromatographic performance of HPLC (isocratic) and UPLC (isocratic) has been obtained by injecting a mixture of stressed solution of Telmisartan (30 µg mL⁻¹). The performance parameters and purity data of both the systems are shown in Table 6. It is observed that the elution time of pure Telmisartan and degradation products in UPLC was reduced by 6-fold to that of isocratic mode HPLC. The resolution and theoretical plates obtained for Telmisartan and degradation products in UPLC showed comparatively better separation efficiency than HPLC. The typical chromatograms obtained from final HPLC and UPLC conditions are depicted in Figure 2.

Conclusions

The newly developed UPLC method for stability indicating assay methods of Telmisartan was found to be capable of giving faster retention times maintaining good resolution than that achieved with conventional HPLC. Stress testing (or forced degradation studies) is an important part of this drug-development process and the pharmaceutical industry has much interest in this area. Although the concept of stress testing is not new to the pharmaceutical industry, the procedure was not clearly defined until the International Conference on Harmonization (ICH) provided a definition in its guidance on stability. The ICH guideline indicates that stress testing is designed to help “To determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used”. In this work a validated stability-indicating method was developed for analysis of Telmisartan in the presence of its degradation products. To best describe the effects of each degradation medium, the effects can be categorized in decreasing susceptibility as alkaline > acidic > oxidative > neutral ~ thermal ~ photo degradation. The specificity and selectivity of the method with the samples under these stresses was demonstrated through the evaluation of RT, RRT, resolution, and purity data for all peaks in the chromatograms using PDA detector. Telmisartan did not degrade on neutral, thermal & photolytic stresses. In a mixture of solution, total four degradation products were formed.

In the present work, a UPLC and HPLC method was used to assess degradation products peaks during a stress testing analysis of Telmisartan drug substance. The newly developed UPLC method for separation of different degradation products along with the pure drug of Telmisartan was found to be capable of giving faster retention times while still maintaining good resolution than that achieved with conventional HPLC. The method was completely validated showing satisfactory data for all the parameters tested. This method exhibited an
excellent performance in terms of sensitivity and speed. It is a stability indicating method suitable for rapid analysis of Telmisartan bulk drug. The method demonstrated linearity over a large range of concentration as automatically calculated by Empower 2. The calibration curve was used to establish the concentration behavior of Telmisartan when subjected to the various stress conditions. The method proved to be simple, accurate, precise, specific and selective. It is hoped that this report on development of a stability-indicating method for analysis of Telmisartan will be helpful for manufacturers of this drug and its combination around the globe by saving them from unnecessarily performing similar studies.

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References

1. ICH (2003) Stability Testing of New Drug Substances and Products Q1A (R2), International Conference on Harmonization, IFPMA, Geneva.
2. ICH (1999) Specifications: Test procedures and acceptance criteria for new drug substances and new drug products, International Conference on Harmonization, IFPMA, Geneva.
3. Dong WM (2006) Modern HPLC for Practicing Scientists, Wiley inter-science: New Jersey, USA.
4. http://pubs.acs.org/subscribe/journals/tcaw/10/i09/html/09dong.html
5. Singh S, Bakshi M (2000) Guidance on conduct of stress test to determine inherent stability of drugs. Pharm Tech On-line 24: 1-14.
6. Sahu K, Patel P, Karthikeyan C, Trivedi P (2010) The ICH guidance in practice: Stress degradation studies on Irbesartan and development of a validated stability-indicating UPLC assay. Acta Chromatogr 22: 189-205.
7. Kapendra S, Chandrabose K, Narayana SHNM Piyush T (2011) A Validated UPLC Method Used for the Determination of Trandolapril and its Degradation Products as per ICH Guidelines. Current Pharmaceutical Analysis 7: 182-188.
8. http://en.wikipedia.org/wiki/Telmisartan
9. http://drugbank.ca/drugs/DB00966
10. Nguyen DT, Guillarme D, Rudaz S, Veuthey JL (2006) Fast analysis in liquid chromatography using small particle size and high pressure. J. Sep Sci 29: 1836-1848.
11. Mazzeo JR, Bao LM, Plumb RS (2005) Advancing lc performance with smaller particles and higher pressure. Anal Chem 77: 460A-467A.
12. de Villiers A, Lestremau F, Szucs R, Gélébart S, David F, et al. (2006) Evaluation of ultra performance liquid chromatography: Part I. Possibilities and limitations. J Chromatogr A 1127: 60-69.
13. Wren SAC, Tchelitcheff P (2006) Use of ultra-performance liquid chromatography in pharmaceutical development. J Chromatogr A 1119: 140-146.
14. Gangola R, Kaushik S, Sharma P (2011) Spectrophotometric Simultaneous Determination of Hydrochlorothiazide and Telmisartan in Combined Dosage Form. Journal of Applied Pharmaceutical Science 01: 46-49.
15. Shen J, Yao Z, Li ZD, Song XJ, Zhong MK (2005) HPLC determination of telmisartan in human plasma and its application to a pharmacokinetic study. Pharmazie 60: 418-420.
16. Wankhede SB, Tajne MR, Gupta KR, Wadodkar SG (2007) RP-HPLC method for simultaneous estimation of telmisartan and hydrochlorothiazide in tablet dosage form. Indian journal of pharmaceutical sciences 69: 298-300.
17. Shah RP, Singh S (2010) Identification and characterization of a photolytic degradation product of telmisartan using LC-MS/TOF, LC-MS², LC-NMR and on-line H/D exchange mass studies. J Pharm Biomed Anal 53: 755-761.
18. http://www.chem.agilent.com/Library/posters/Public/ASMS_2011_MP_181.pdf
19. Bakshi M, Singh S (2002) Development of validated stability-indicating assay methods-critical review. J Pharm Biomed Anal 28: 1011-1040.
20. Singh S, Singh B, Bahuguna R, Wadhwala L, Saxena R (2006) Stress degradation studies on ezetimibe and development of a validated stability-indicating HPLC assay. J Pharm Biomed Anal 41: 1037-1040.