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Solid State Form of Azilsartan Kamedoxomil and Process for its Preparation

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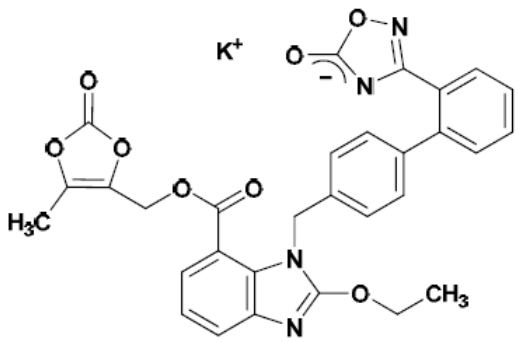
Introduction:

Azilsartan kamedoxomil is the potassium salt of Azilsartan medoxomil. Azilsartan medoxomil, a prodrug, is hydrolyzed to Azilsartan in the gastrointestinal tract during absorption. Azilsartan is a selective AT1 subtype angiotensin II receptor antagonist.

Azilsartan kamedoxomil is represented by the following structural formula;



Azilsartan kamedoxomil

The chemical name of Azilsartan kamedoxomil is (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate monopotassium salt.

Azilsartan kamedoxomil is approved by USFDA on Feb 25, 2011 and is being sold under the brand name Edarbi.

Edarbi is an angiotensin II receptor blocker indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Edarbi may be used, either alone or in combination with other antihypertensive agents.

Solid form screening is carried out on Azilsartan kamedoxomil using various solvents.

Provided herein is a solid state form of Azilsartan kamedoxomil and process for its preparation.

Solid state form of Azilsartan kamedoxomil:

The authors of the present publication provided a solid state form of Azilsartan kamedoxomil designated herein as crystalline Form-M and process for its preparation.

The crystalline Form-M of Azilsartan kamedoxomil is characterized by its PXRD (Powder X-Ray Diffraction) pattern having peaks at 6.1, 12.1, 18.6 and 19.3 ± 0.2º of 2θ.

The measurements of the PXRD peak locations (2θ values) and/or intensity will vary within a margin of error. The margin of error for 2θ values is ± 0.2º.

The crystalline Form-M of Azilsartan kamedoxomil described herein is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used.

Experimental procedure:

Preparation of crystalline Form-M of Azilsartan kamedoxomil:

Crystalline Form-M of Azilsartan kamedoxomil is prepared as follows:

50 gm of Azilsartan kamedoxomil is dissolved in 250 ml of dimethyl sulfoxide at 25-30ºC. The obtained solution is added to 2.25 Lt of pre-heated ethyl acetate at 50-55ºC and stirred the mixture for 45 min at the same temperature. Slowly cooled the mixture to 25-30ºC and stirred for 1 hr at the same temperature. Slowly heated the mixture to 50-55ºC and stirred for 1 hr at the same temperature. Cooled the mixture to 25-30ºC and stirred for 1 hr at the same temperature. The resulting precipitate is filtered and washed with ethyl acetate. The solid obtained is dried to afford 32.2 gm (64.4%) of Azilsartan kamedoxomil as a crystalline solid.

Purity by HPLC: 99.32%

Ethyl acetate content: 33892 ppm

Moisture content: 0.26%.

Particle size distribution: D(10): 18 µm, D(50): 63.9 µm, D(90): 170.9 µm.

The authors have analyzed the crystalline Form-M of Azilsartan kamedoxomil obtained by the above process by various techniques viz., PXRD, DSC, TGA, ^{13}C solid state NMR, ^{1}H NMR etc., to determine the characteristics of the solid form obtained and the results are provided below.

Results and Discussion:

PXRD (Powder X-Ray Diffraction) Studies:

The results of PXRD analysis revealed that Azilsartan kamedoxomil prepared according to the above described process is crystalline in nature. The resulting PXRD pattern is presented in Figure-1.

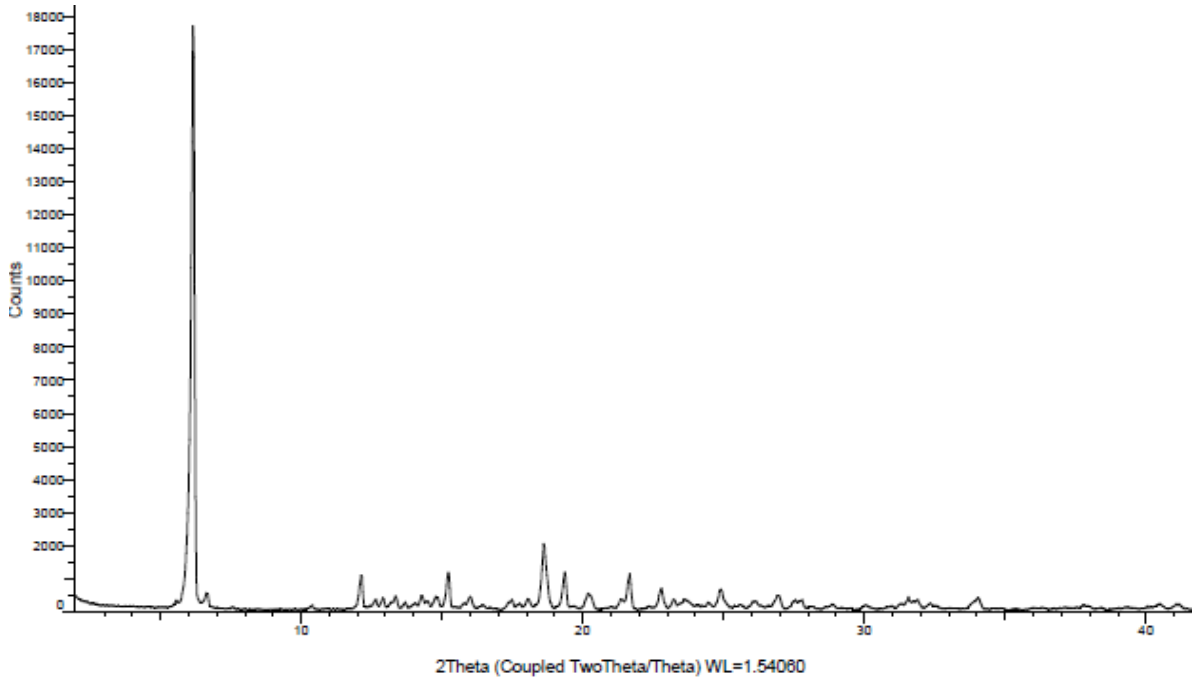


Figure-1: *Powder X-Ray diffraction (PXRD) pattern of Azilsartan kamedoxomil Form-M*

PXRD peak listing for crystalline Form-M of Azilsartan kamedoxomil is provided in Table-1.

Table-1: PXRD peak listing for Azilsartan kamedoxomil crystalline Form-M

S.No	2θ value
1	6.1
2	6.6
3	12.1
4	12.6
5	12.9

6	13.3
7	14.3
8	14.4
9	14.8
10	15.2
11	15.9
12	18.0
13	18.6
14	19.3
15	20.2
16	21.4
17	21.6
18	22.7
19	24.9
20	26.9
21	27.5

DSC (Differential Scanning Calorimetry):

DSC thermogram of Azilsartan kamedoxomil showed two endotherms, one at 180.06°C and the other at 228.02°C. The first endotherm is due to desolvation (ethyl acetate) and second endotherm is due to melting of Azilsartan kamedoxomil. Results of DSC analysis are shown in Figure- 2.

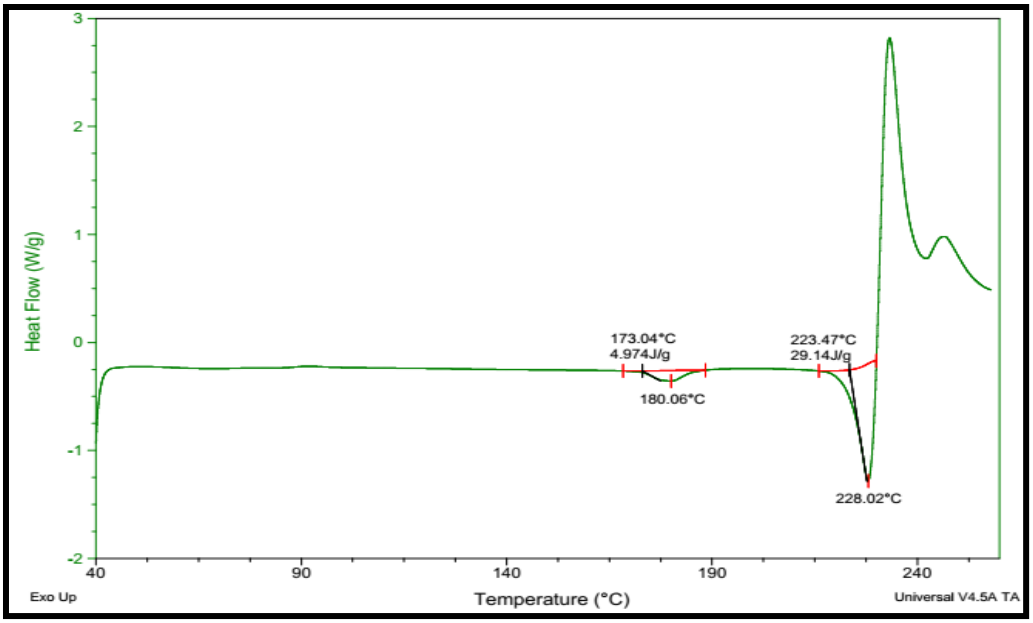


Figure-2: *Differential scanning calorimetric (DSC) thermogram of Azilsartan kamedoxomil Form-M*

TGA (Thermogravimetric Analysis):

Thermal analysis (TGA) of Azilsartan kamedoxomil showed two weight loss events. The first weight loss event from 25-100°C is due to surface water and solvent loss which is 0.265%. The second weight loss event from 150-190°C is corresponding to ethyl acetate solvent loss which is about 2-3%. The results of TGA analysis are presented in Figure-3.

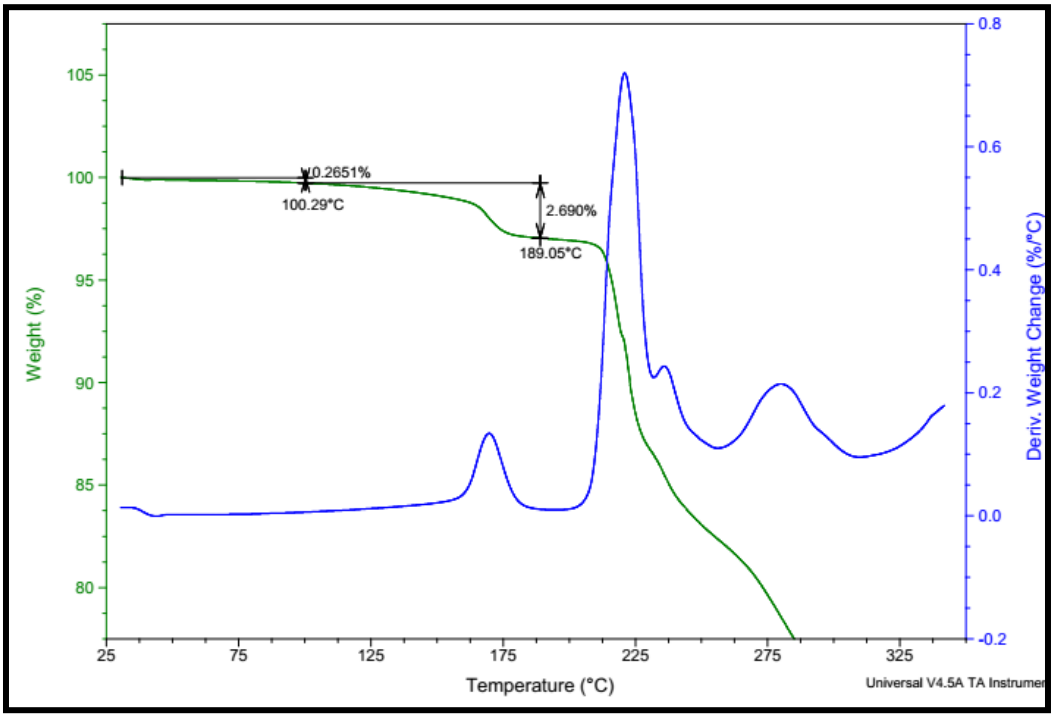


Figure-3: *Thermogravimetric analysis (TGA) curve of Azilsartan kamedoxomil Form-M*

Based on the above DSC and TGA results, the weight loss or desolvation at higher temperature than the boiling point of solvent (ethyl acetate) reveals that the solvent is present in the crystal lattice. RS/OVI results of Form-M are also evident for the presence of ethyl acetate solvent in the sample.

^{13}C Solid state NMR:

The solid state Form-M of Azilsartan kamedoxomil is further analyzed by ^{13}C solid state NMR technique and the results are provided in Figure-4.

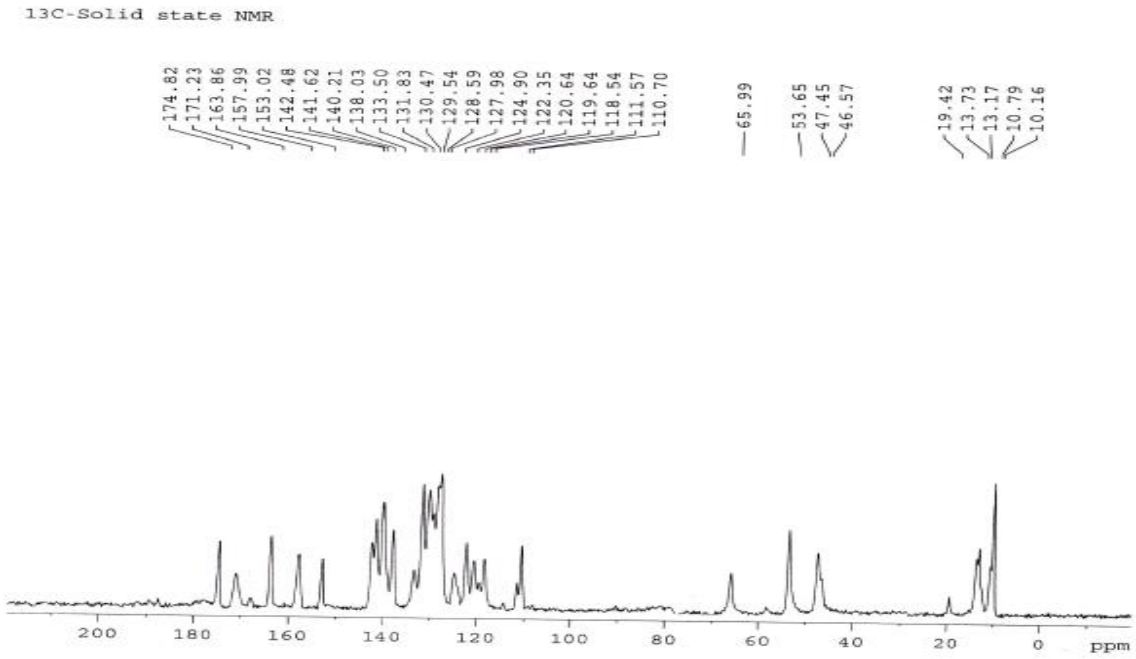


Figure-4: *^{13}C solid state CP-MAS NMR spectrum of Azilsartan kamedoxomil Form-M*

^{1}H NMR:

The authors have analyzed the sample obtained from the above described process by using ^{1}H NMR (solution state). In the ^{1}H NMR spectrum, the authors have observed the ethyl acetate protons at δ= 1.15-1.19 (-CH3), 1.98 (-COCH3) and 4.0-4.05 (-CH2) ppm. The resulting spectrum is provided in Figure-5.

The authors have heated the sample to 180°C and cooled back to 25°C using TGA instrument. The resulting sample is analysed by ^{1}H NMR. The authors have observed the absence of ethyl acetate protons in ^{1}H NMR at their respective δ ppm positions. The resulting spectrum is provided in Figure-6.

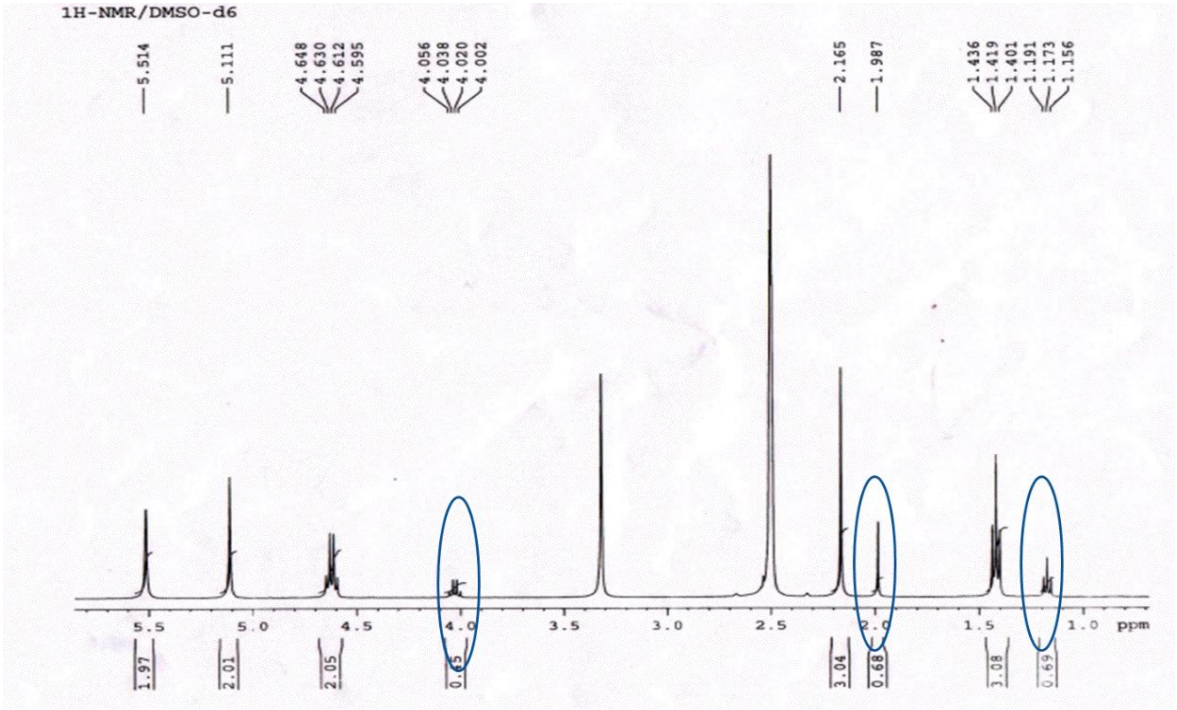


Figure-5: *^{1}H NMR spectrum of Azilsartan kamedoxomil Form-M*

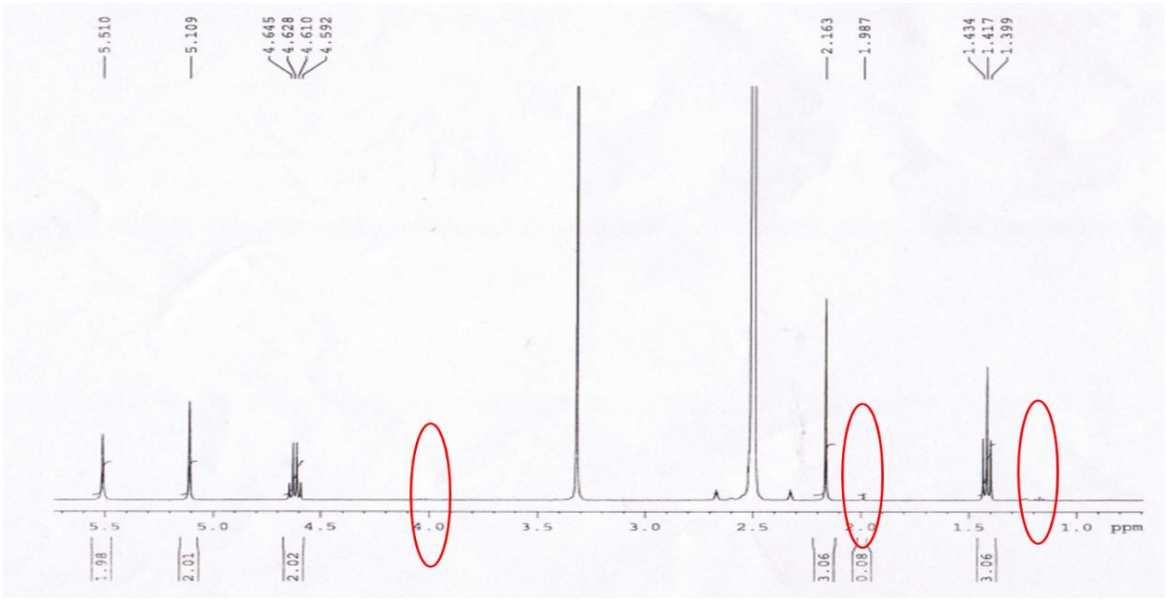


Figure-6: *^{1}H NMR spectrum of Azilsartan kamedoxomil Form-M (heat-cooled from 180 to 25°C)*

The ^{1}H NMR spectra results reveal that the solvent ethyl acetate is present in the crystal lattice of the sample.

Microscopic image:

Microscopic image of the solid isolated from the above process is provided in Figure 7. The particles isolated are larger in size and are suitable for the preparation of various pharmaceutical formulations. The D_{90} of the solid form isolated is found to be > 100 µm.

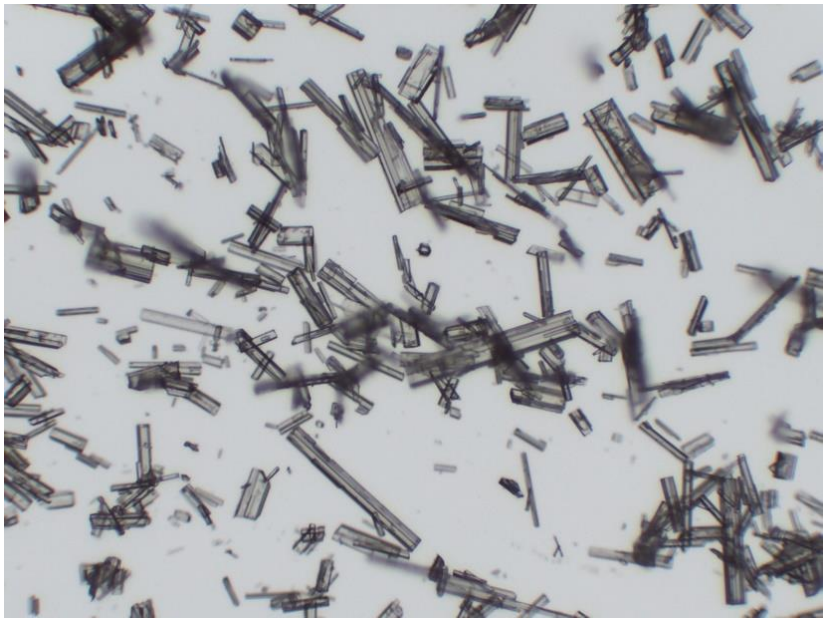


Figure-7: *Microscopic image of Azilsartan kamedoxomil Form-M*

The solid state form of Azilsartan kamedoxomil obtained by the above described process is found to be an ethyl acetate solvated form which is supported by the above analytical results.

Methods of Analysis and Equipment:

The PXRD analysis is carried out by using BRUKER/D8 ADVANCE X-Ray diffractometer using CuKα radiation of wavelength 1.5406A° and at a continuous scan speed of 0.03°/min.

The differential scanning calorimetric (DSC) analysis is performed on a TA instrument DISCOVERY DSC 25 (USA) with aluminium pans. Samples held in a closed pan are analyzed at a heating rate of 10°C/min under nitrogen atmosphere.

The thermogravimetric (TGA) analysis is performed on a DISCOVERY TGA 550 instrument with platinum pan.

Microscopic image is taken from MOTIC microscope model BA 410E using 10X magnification.

^{1}H NMR (400 MHz) & ^{13}C solid state CP-MAS NMR (100 MHz) are captured by using BRUKER AVANCE III HD instrument.

Azilsartan kamedoxomil is analyzed by HPLC under the following conditions;
Apparatus: A liquid chromatographic system equipped with variable wavelength UV-detector and integrator; Column: YMC Pack Pro C18, 150 x 4.6 mm, S-3µm,12 nm or Equivalent; Wavelength: 220 nm; Column temperature: 25°C; Injection volume: 5 µL; Diluent: Chilled acetonitrile (100%); Elution: gradient; Buffer: Weigh accurately 2.72 g of potassium dihydrogen orthophosphate and 4.0 g 1-Octane sulphonic acid sodium salt anhydrous and dissolve in 1000 mL of Mill-Q water, adjust pH to 2.5 with dilute Ortho phosphoric acid. Filter this solution through 0.22 µm PVDF membrane filter paper and sonicate to degas. Mobile phase-A: Buffer (100%); Mobile phase-B: Acetonitrile: water (90:10) v/v; Auto sampler temperature: 5°C.