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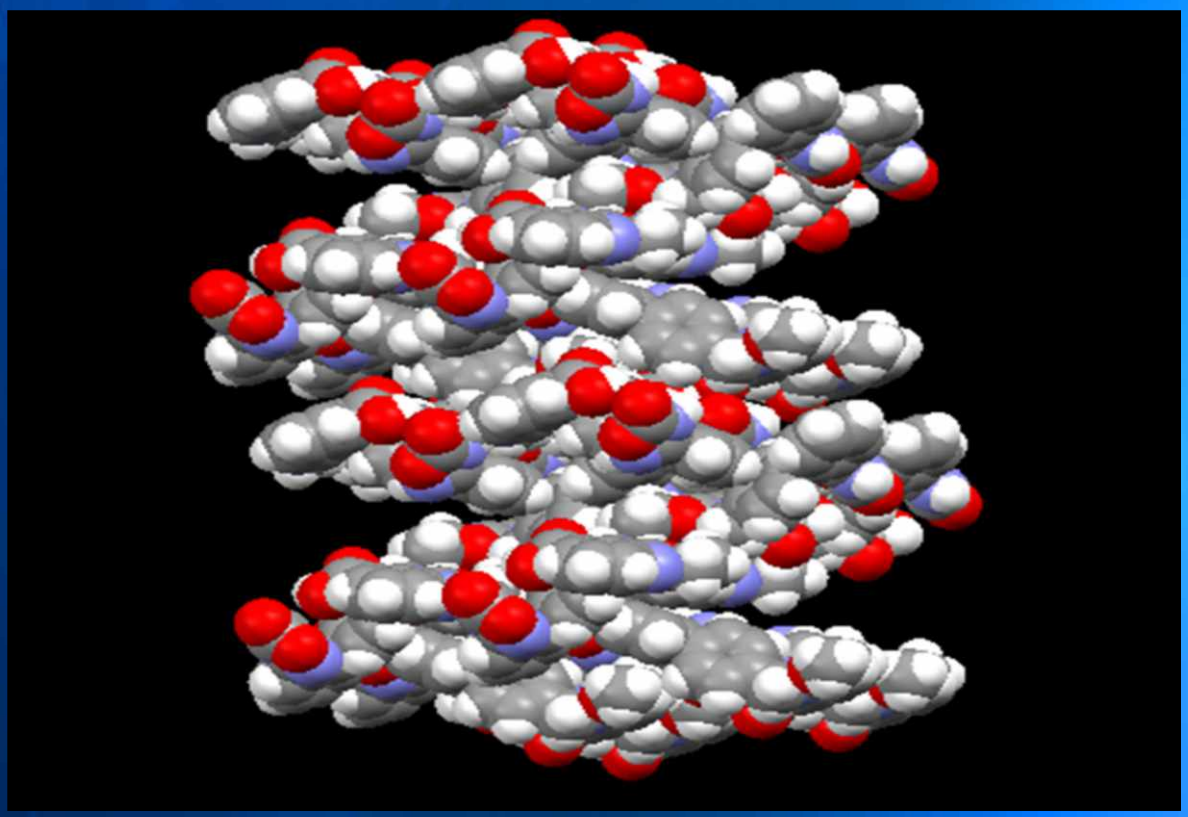

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Its mechanism is the selective block of the binding of angiotensin II with receptor AT_1 and thus the resulting. It can be prescribed as a treatment for hypertension by itself or in com-bination with other anti-hypertension drugs, blood vessel constriction [1]. It does not function through the biosynthetic pathway of an-giotensin II, thus avoids affecting the concentration of bradykinin as ACE inhibitors. Azilsartan has no common side effects such as dry cough [2].

Different types of crystals from the same drug can have different solubility and absorbility in our body and thus impact on its clinical efficacy and safety. Therefore, crystal types may directly affect the quality and efficacy of drugs. The study of the polymorphiccrystal types of Azilsartan will facilitate the improvement of its stability during preparation and storage. The research will also help to improve the bioavailability and efficacy and to reduce toticity [3].

Azilsartan is a white powder. Four types of crystalline powder have been reported with respective melting points (mp) of 122 - 123 (type III), 163 - 164 (type II), 180 - 181 (type IV), and 198˚C - 206˚C (type I) [4]-[6]. The preparation of type II and III crystals has been reported [4] [6]. Type II crystal is obtained from DMF and acetone; whereas type III crystal is from DMF and isopropanol. The preparation of type IV crystal from THF has also been reported [5]. However, only powder diffraction data for these crystal types have been reported and no single crystal diffraction data are available. Furthermore, the stability and solubility of these crystal types have not been carefully investigated.

We have obtained type I crystal of Azilsartan from methanol. The crystals melt at 198˚C - 201˚C and are not hydroscopic. The advantage of this method is the low toxicity of methanol solvent and thus the suitability for pharmaceutical application. We analyze the single crystal diffraction, measure the solubility of type I and II crystals in methanol with HPLC, determine their G_T values under different temperatures, and compare their stability.

2. Experimental

2.1. Reagents and Instruments

All reagents were analytical pure grade and were used without further purification. Melting points were determined using microscopic melting point apparatus. Single crystal diffraction data were obtained with Enraf-Nonius CAD4 X-ray diffractometer. Powder diffraction data were obtained with Bruker D8-Discover X-ray diffractometer. DSC data were obtained with Mettler-Toledo differential scanning calorimeter (the rate of heating is 10˚C/min).

2.2. Preparation of Azilsartan Type I and II Crystals

Type I crystal: Methanol (100 mL) was added to an Erlenmeyer flask containing Azilsartan (2 g) and the mixture was stirred for 30 minutes. Another 100 mL of methanol was added to obtain a clear solution. To another flask was added 30 mL of the above clear solution, added 0.1 g valine, 6 mL water, and 5 mL methanol. The mixture was stirred for 30 minutes to obtain a clear solution. After two weeks,colorless crystals (0.13 g, mp 198˚C - 201˚C) were obtained.

Type II crystal: Type II crystals were prepared as white powder (mp 164 - 166) according to reported.

2.3. Structural Determination of Azilsartan Type I Crystals

All data were obtained at 20˚C under MoKa ray (λ = 0.71073 Å) and ω-scanning method. Structure was solved and refined with SHELXL-97. Single crystal diffraction data were summarized in **Table 1**.

2.4. Determination of the Solubilities of Azilsartan Type I and II Crystals in Methanol

Sample Preparation: The powdered crystals (0.5 g) were each added to a flask with 15 mL methanol. The mixture was heated to 55˚C and the temperature was maintained for 1 hour. An aliquot (10 μL) of the solution was taken and mixed with 10 mL of the HPLC eluent (discussed below). This solution was further diluted with the same eluent (1 mL solution with 3 mL eluent) and filtered. The original sample solution in methanol was cooled to 50˚C, 45˚C, 40˚C, 35˚C and 30˚C. Samples at each temperature were prepared in the same manner.

Measurement: Measurement was done at 253 nm using WUFENGLC100 HPLC with reverse phase C18 column, eluent acetonitrile: water: acetic acid (57:43:1 by volume), temperature 30˚C, flow rate 1.0 mL/min [7].

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