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# Crystallization of R-(+)-atenolol hydrochloride from racemic ionic liquid - A selective double decomposition green reaction

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ABSTRACT

Atenolol is a cardioselective antihypertensive drug. It is classified under arylethanolamine β adrenergic receptor antagonists. Hypotensive action for this racemic drug was found to be selective for the S-(−)- β receptor blocking stereoisomer as this enantiomer was found to have 20 fold greater affinity for $\beta_1$ adrenoreceptors when compared to $\beta_2$ adrenoreceptors of human heart muscle. Albeit the action of the drug was mentioned as stereoselective, atenolol is always administered as racemic mixture only. Recently several adverse drug reports were published on atenolol treatment and the study suggested for intensive research on structure activity relationship of R-(+)-stereoisomer. In this study, we report the solid state structure of R-(+)-atenolol for the first time as hydrochloride salt. We also report a unique resolution process based on ionic liquid formation for obtaining this stereoisomer. The process is first of its kind for a pharmaceutical ionic liquid material. We believe that the atomic structure of R-(+)-stereoisomer will significantly contribute for understanding its biological activity when compared to its counter enantiomer.



## 1. Introduction

Molecular liquids have become most interesting materials for research and applications in biology and physical sciences. Molecular liquids are produced by the physical interaction of two solids at room temperature. Ionic liquids are a class of molecular liquids. Ionic liquids (ILs) are claimed to have wide range of applications that include difosol process [1], ionikylation [2], cellulose processing [3], nuclear fuel processing [4], waste recycling [5], extraction of natural products [6] and battery life enhancement [7] etc. The term "ionic liquids" refers to liquids composed entirely of ions that are fluid around or below 100 °C [8]. Pharmaceutical ionic liquids are relatively new. Research on pharmaceutical ionic liquids as novel drug delivery dosage forms is enduring and awaits for standard analytical and assay procedures for the drug content. As majority of the Active Pharmaceutical Ingredients (APIs) are weak bases and acids, ionic liquid form for good number of APIs is possible. APIs in ionic liquid form have several advantages like shelf life improvement and facilitated bioavailability [9]. Further, it was also demonstrated that ionic liquids are good and environment safe materials for extraction, synthesis and purification of APIs. Ionic liquids for racemic modification is another important application for it in chiral synthesis. A good number of racemic mixtures are resolved using ionic liquid materials [8,10,11]. In this paper we report the formation of a pharmaceutical ionic liquid which is composed of RS-atenolol and D-(+)-malic acid. Further, we also report how a stereoselective separation of R-(+)-Atenolol was performed on this ionic liquid.

Atenolol ((RS)-2-{4-[2-Hydroxy-3-(propan-2-ylamino)propoxy] phenyl} acetamide) is a cardioselective antihypertensive drug. It is classified under arylethanolamine β adrenergic receptor antagonists. Hypotensive action for this racemic drug was found to be selective for the S-(−)- β receptor blocking stereoisomer as this enantiomer was found to have 20 fold greater affinity for $\beta_1$ adrenoreceptors when compared to $\beta_2$ adrenoreceptors of human heart muscle [12]. No significant difference was observed in pharmacokinetics for the enantiomers except with their renal clearance. S-(−)-enantiomer had shown relatively more renal clearance when compared with its antipode [13]. Albeit the action of the drug was mentioned as stereoselective, atenolol is always administered as

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racemic mixture only. Recently several adverse drug reports were published on atenolol treatment and the study suggested to forbid the atenolol containing formulations [14–17]. It is believed that adverse reactions of racemic drugs are often associated with one particular stereoisomer. It is therefore important to investigate the pharmacological behaviour of individual isomers of atenolol and establish the enantiomer activity relationship.

Few studies reported that R-(+)-atenolol has no significant biological role, while other reported the binding of R-(+)-stereoisomer with some biological proteins like $\beta_2$ adrenergic receptors [14], phospholipase A2 [18] and lactoferrin [19]. From literature it is clear that no concrete conclusion is made till date on the pharmacological activity of R-(+)-isomer. Therefore, a thorough research should be conducted on resolution of enantiomers and determine the structure and activity relationship of R-(+)-stereoisomer. Several papers were published on resolution of atenolol. Majority of the methods involve impregnated TLC and chiral chromatography [20–25]. A kinetic resolution method was also reported for synthesizing the bioactive isomer [26]. X-ray crystal structures of (RS)-atenolol and S-(−)-atenolol were reported considering their biological importance [27]. No crystal structure reports were found on R-(+)-atenolol except as in complex with the above mentioned biological protein molecules [18,19].

In this study, we report the solid state structure of R-(+)-atenolol for the first time as hydrochloride salt. We also report a unique resolution process based on ionic liquid formation for obtaining this stereoisomer. The process is first of its kind for a pharmaceutical ionic liquid material.

## 2. Materials & methods

### 2.1. Process for the preparation of atenolol hydrochloride crystals

Atenolol (1 g, 3.75 mmol) was mixed with equimolar proportion of D-(+)-malic acid (0.503 g, 3.75 mmol). A dense liquid material that was formed upon mixing was kept in a clean & dried petridish. Sodium chloride crystals in equimolar quantity were added and the material was kept aside for observation. A slow crystallization of a part of the material was observed and the crystalline solid was separated from the material on filter paper. The crystals were washed thoroughly with chloroform and air dried.

**Table 1**
Properties of (RS)-Atenelol/D-(+)-Malic acid ionic liquid.

| Property | Value |
|---|---|
| Melting point (°C) | −3.55 |
| Freezing point (°C) | −22.65 |
| Glass transition temperature (°C) | −65.07 |
| Onset of thermal decomposition (°C) | 230 |
| Viscosity (cP, 25 °C) | 650 |
| Density at 25 °C, kg/m3 | 1214 |

### 2.2. Ionic liquid characterization

The intermediate material, ionic liquid, was characterized for various thermal properties like melting point, crystallization point and glass transition point using DSC. The stability of the liquid was characterized by decomposing the material using TGA. Viscosity of the liquid was measured by viscometer. Density was measured by using specific gravity method.

### 2.3. Characterization of R-(+)-Atenelol hydrochloride

R-(+)-Atenolol Hydrochloride crystals were characterized for elemental composition using Perkin-Elmer 2400 Series CHNS/O Analyser. IR absorbance for the compound was analyzed at band width 400–4000 $cm^{-1}$ using Perkin Elmer Paragon 1000 FT-IR spectrometer. Molecular weight of the compound was determined by using Mass spectrophotometer. Single crystal X-ray diffraction data were collected by Oxford Diffraction Xcalibur CCD diffractometer with graphite-monochromated Mo $K\alpha$ radiation at 293 K using $\omega$-scans at the crystal to detector distance of 50 or 60 mm. Programs CrysAlis CCD and CrysAlis RED were employed for data collection, cell refinement and data reduction. Structure solution calculations were performed with SHELXS97 and SHELXL97 [28] (both operating under the WinGX [29] program package). Geometry calculations were done using PLATON [30] and PARST [31], and the molecular graphics were done with ORTEP [32] and Mercury [33]. Powder X-ray diffraction (PXRD) patterns were measured using a Phillips X'Pert Pro diffractometer. Samples were gently flattened onto a zerobackground silicon holder. A continuous 2θ scan range of 2°–35° was used with a Cu Kα radiation source and a generator power of 40 kV and 40 mA. A step size of 0.0167° per 2θ with a step time of 10.16 s was used. Samples were rotated at 25 rpm and all experiments were performed at room temperature. DSC analysis was performed on the samples using a TA Instruments Q500 system, again using a 10 °C/min heating rate. The DSC sample sizes were in the range of 3–10 mg. Specific rotation of the product was meassured by polarimeter.

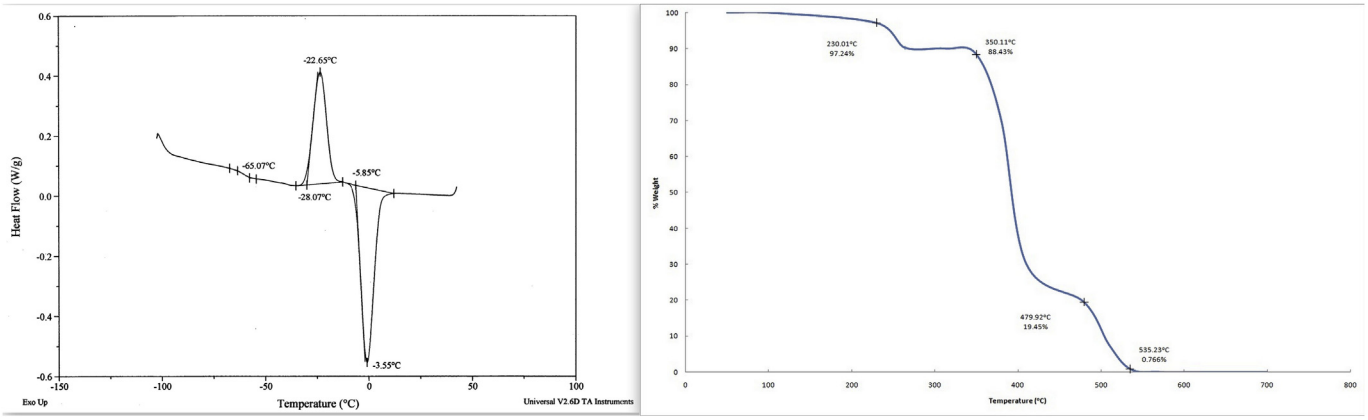


**Fig. 1.** DSC & TGA thermogram for the (RS)-Atenelol/D-(+)-Malic acid ionic liquid.