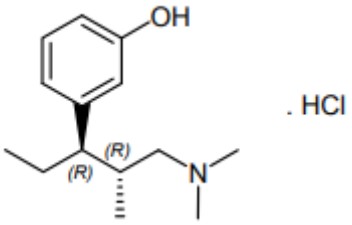
March 2022

Process for the preparation of Tapentadol hydrochloride

Process for the preparation of Tapentadol hydrochloride

Tapentadol hydrochloride of formula I, a centrally-acting analgesic compound, is chemically known as 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride and marketed under the trade name Nucynta®.



Tapentadol and its analogues were disclosed in US patent 6,248,737 herein referred as US‘737 (reissue as USRE 39,593). According to the process disclosed in this patent, tapentadol hydrochloride is prepared by demethylation of (2R,3R)-3-(3-methoxyphenyl)-N,N-2-trimethylpentan-1-amine hydrochloride by using hydrobromic acid to give tapentadol free base as a residue. The obtained residue is dissolve in 2-butanone followed by addition of trimethylchlorosilane and water to afford tapentadol hydrochloride.

The present invention provides the alternative process for the preparation of Tapentadol hydrochloride. The intermediate (2R,3R)-3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride used in the preparation of Tapentadol hydrochloride can be prepared by process described in US‘737 (reissue as USRE 39,593) or by the process described in the literature.

Example 1: Preparation of Tapentadol hydrochloride

Mixture of (2R,3R)-3-(3-methoxyphenyl)-2-methylpentyl]-dimethylamine hydrochloride (100 g) and hydrobromic acid (250 ml) at 25-30°C at 25-30°C heated to 110-115°C and stirred at the same temperature. The resulting mixture cooled to 40-45°C and water added to it. Basified using ammonia solution (250 ml) and stirred at the same temperature. Toluene added to the mixture at 25-30°C and stirred at the same temperature. Separated the layers, extracted the aqueous layer with toluene. Combined the organic layers was washed with water. The obtained organic layer was extracted into aqueous acetic acid solution. Further, toluene added to obtained acetic acid layer and basified by using aqueous ammonia solution. Separated the organic layer from the mixture and the aqueous layers was extracted with toluene. Combined the organic layers and was washed with water. Obtained organic layer

contains Tapentadol free base and the same was converted into Tapentadol HCl by using isopropanolic hydrochloric acid.

Example 2: Preparation of Crystalline form-A of Tapentadol hydrochloride

Dissolved Tapentadol HCl (50 g) in the mixture of 2-butanone (70 ml) and water (17 ml) at 70-75°C. Filtered the obtained solution for particle free and washed with 100 ml of the mixture of 2-butanone and water. The obtained filtrate was stirred at 70-75°C and 2-butanone was slowly added to it at the same temperature. Cooled the mixture to 0-5°C and stirred. Filtered the precipitated solution, washed with 2-butanone and dried to get the title compound.

***