Problem solving in Pharmaceutical processes: isolation, characterization and synthetic preparation of unknown impurities in 4-piperidinepropanol manufacture.

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Impurity management is a common practice in the pharmaceutical manufacture. Every time a new synthetic route is being developed, unknown impurities can pose in serious jeopardy the whole process. The identification of present impurities, and even more the understanding of their formation pathways, may enable the implementation of changes to the process to avoid problems in subsequent steps, not limited to the control of the residual impurities on the finished product. An emblematic case is here presented to show a fast response approach to a complex issue.
4-piperidinepropanol is a well-known building block, for example in the preparation of polysulfonamides [1], polyurethane polymers [2], as a synthetic reagent for the preparation of thrombin inhibitor [3], effective as a therapeutic or prophylactic agent for conditions such as depression, anxiety, Alzheimer's disease [4], or for the preparation of cardiotonic agents [5]. Our interest in such a small and simple molecule pushed us to search for our own synthetic preparation (Figure 1) [6]. However, in the manufacturing campaign of this intermediate, a new unknown impurity was detected and found to be critical (Figure 2). Since it was higher than our specification limit (0,1% for every single UK impurity), its identification (Figure 3) and other corrective actions were required . The strategy for impurity management applied and here described allowed changes to be implemented in subsequent batches, solving the problem at its root.

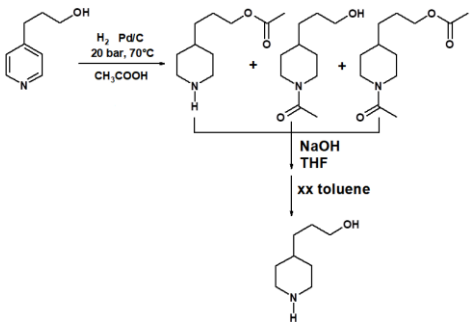

Figure 1

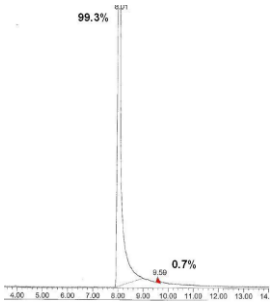

Figure 2

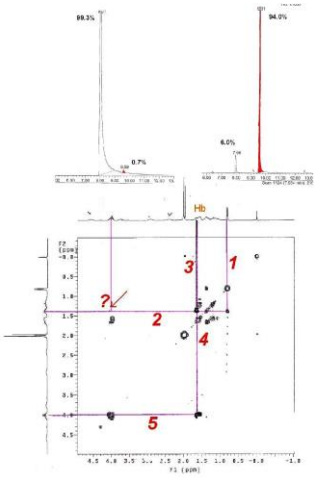

Figure 3

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