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"DETERMINATION OF METHYL PARA TOLUENE SULPHONATE IN APREPITANT USING UPLC METHOD"

Sowmya A [*1] and Suresh babu M[2]

*[*1]Department of Pharmaceutical chemistry, Sri Siddhartha College of Pharmacy, Nuzivid, Andhra Pradesh*
[2]Department of Pharmaceutical analysis, JITS College of Pharmacy, Kalagampudi, Palakollu, Andhra Pradesh
Email id: adapa.sowmya@gmail.com

Abstract: Impurity is defined as any substance coexisting with the original drug. Control of toxic impurities in drug substances has received more and more attention over the past years. These are to be determined based on the maximum daily dose. According to EMEA guidelines, a TTC value of 1.5 microgram/day intake of a toxic impurity is considered to be associated with an acceptable risk. The concentration limits in ppm of permitted toxic impurity in a drug substance is the ratio of TTC in microgram/day and daily dose in gram/day. Impurities present in excess of 0.10% should be identified and quantified by selective methods. In Aprepitant (APT) drug substance, Methyl-p-toluene sulphonate (MPTS) was suspected to carried from raw materials. The maximum daily dose of Aprepitant is 125 mg /day. From this TTC level has found to be 12ppm. In literature, no method was reported for the determination of this impurity. From the above calculation, the present studies are aimed towards the determination of this compound in Aprepitant at the level of 12 ppm (lower end) by Ultra Performance Liquid Chromatography. And the proposed UPLC method was validated as pre-ICH Guidelines and the following parameters are studied System Suitability, Specificity, LOD, LOQ, Linearity, Batch analysis, Precision, LOQ recovery, LOD recovery.

Key words: Ultra Performance Liquid Chromatography, Aprepitant, impurity

INTRODUCTION

Chromatography may be regarded as "an analytical technique employed for the purification and separation of organic and inorganic substances". It is also found useful for the fractionation of complex mixture and separation of closely related compounds such as isomers and isolation of unstable substances. Chromatography technique is based on the difference in the rate at which the components of a mixture move through a porous medium (stationary phase) under the influence of some solvent or gas (mobile phase). Chromatography techniques are roughly classified on the basis of purpose for which they are used and method developed. The different types of laboratory techniques used in the separation of mixtures are grouped under an umbrella term,

chromatography. The process through which constituents of a mixture are separated and analyzed by physical means is referred to as chromatography. Apart from the different criteria of classification of chromatography discussed below, the basic criterion is the purpose for which this process is carried out. On the basis of this criterion, the process of chromatography is classified into analytical and preparative. The former is carried out for the purpose of measuring the amount of an analyte present in a mixture. On the other hand, preparative chromatography is used for separating the components of a mixture for their further use. Depending on the techniques used in chromatography, the process is broadly classified as adsorption and partition chromatography.

An impurity in a drug substance as defined by the International Conference on Harmonization [7] (ICH) Guidelines is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product. Therefore, any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties. The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Most of the Active Pharmaceutical Ingredients (APIs) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components can be generated during such a process[8]. Those components remaining in the final API are considered as impurities. The sources and routes of formation of impurities in generics are special case, they are the same as those in the reference drug product: starting materials, by-products and residual solvents from the API synthesis; degradants formed during the process and long-term storage; contaminants from packaging components and other drug products manufactured in the same facility. Impurities could be forming from the impact of heat, light, and oxidants (including air) on the drug product and might be catalyzed or accelerated by trace metal impurities[9] changes in the pH of the formulation, interactions with packaging components, excipients and other active ingredients, in the case of combination products. Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an important part of drug development and regulatory assessment.

It is frequently necessary to isolate and characterize impurities in order to monitor them accurately, because approximate estimations of impurities are generally made against the material of interest (i.e. drug substance) and can be incorrect. These estimations are based on the assumption that impurities are structurally related to the material of interest and thus have the same detector response. It is important to test this assumption because impurities frequently have different structures with significantly different detector responses. Most of the time it is difficult to ensure that the assumption stated above is correct. Number of methods can be used for isolation and characterization of impurities. But the application of any method depends on the nature of impurity (i.e.) its structure, physicochemical properties and availability Qualification is the process of

acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) being considered. When appropriate, we recommend that applicants provide a rationale for establishing impurity acceptance criteria that includes safety considerations. An impurity is considered qualified when it meets one or more of the following conditions: a. When the observed level and proposed acceptance criterion for the impurity do not exceed the level observed in an FDA approved human drug product, b. When the impurity is a significant metabolite of the drug substance, c. When the observed level and the proposed acceptance criterion for the impurity are adequately justified by the scientific literature d. When the observed level and proposed acceptance criteria for the impurity do not exceed the level that has been adequately evaluated in comparative in vitro genotoxicity studies.

EMEA guideline on the limits of genotoxic impurities, became effective on January 1st, 2007, recommends dichotomizing GTIs into those for which there is 'sufficient (experimental) evidence for a threshold related mechanism' and those 'without sufficient (experimental) evidence for a threshold related mechanism.' Those GTIs with sufficient evidence would be regulated using methods outlined in ICH Q3C(R4) for class 2 solvents. For genotoxic impurities without sufficient evidence for a threshold related mechanism, the guideline proposes a policy of controlling levels to 'as low as reasonably practicable' (ALARP principle). Although this approach is acceptable in most instances, mechanistic data sufficient to allow for an assessment of threshold mechanism is lacking. Hence, guideline proposed the use of a 'threshold of toxicological concern (TTC)', which refers to a threshold exposure level to compounds that will not pose a significant risk of carcinogenicity or other toxic effects. A TTC value of 1.5 microgram/day intake of a GTI is considered to be associated with an acceptable risk. The concentration limits in ppm of permitted GTI in a drug substance is the ratio of TTC in microgram/day and daily dose in gram/day. The TTC approach benefits consumers, industry and regulators by avoiding unnecessary extensive toxicity testing and safety evaluations.

Aprepitant [19], an antiemetic, is a substance P/neurokinin 1 (NK1) receptor antagonist which, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors. Aprepitant has little or no affinity for serotonin (5-HT3), Dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-Induced nausea and vomiting (CI NV). Aprepitant[20] is a selective high-affinity antagonist of human substance P/neurokinin 1(NK)receptors. Aprepitant has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV). Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such ascisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain

NK1receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acuteand delayed phases of cisplatin-induced emesis.

MATERIALS AND METHODS

Preparation of Solvent: Dissolved 0.77 g of Ammonium acetate in 1000 ml of water. Adjusted to 3.0 with orthophosphoric acid. Prepare mixture of buffer and acetonitrile in the ratio of 30:70v/v was used as solvent.

Preparation of Blank solution: Use solvent as blank solution.

Preparation of MPTS Individual Stock Solutions (100 ppm): Weighed accurately about 10.0 mg of MPTS into separate 100ml volumetric flasks, dissolved and diluted to volume with diluent and mixed. Diluted 1.0 ml of each solution separately to 100 ml with solvent.

Preparation of APT Test Solution (10 mg/ml): Weighed accurately about 100 mg of the test sample into a 10 ml volumetric flask, Dissolved and diluted to the volume with solvent and mixed.

Preparation of HAPTRC0$_2$ Standard stock solution (100ppm): Weighed accurately about 10mg of HAPTRC0$_2$ into 100 ml of volumetric flask, dissolved and diluted to volume with solvent and mixed. Diluted 1 ml of this solution to 100 ml with solvent.

Preparation of HAPTRC0$_2$ Standard solution (12ppm): Take 2.4 ml of standard stock solution (100ppm) into a 20 ml volumetric flask containing solvent and diluted to volume with solvent and mixed.

Preparation of HAPTRC0$_3$ Standard stock solution (100ppm): Weighed accurately about 10mg of HAPTRC03 into 100 ml of volumetric flask, dissolved and diluted to volume with solvent and mixed. Diluted 1 ml of this solution to 100 ml with solvent.

Preparation of HAPTRC0$_3$ Standard solution (12ppm): Take 2.4 ml of standard stock solution (100ppm) into a 20 ml volumetric flask containing solvent and diluted to volume with solvent and mixed.

Preparation of HAPTRC0$_4$ Standard stock solution (100ppm): Weighed accurately about 10mg of HAPTRC04 into 100 ml of volumetric flask dissolved and diluted to volume with solvent and mixed. Diluted 1 ml of this solution to 100 ml with solvent.

Preparation of HAPTRC0$_4$ Standard solution (12ppm): Take 2.4 ml of standard stock solution (100ppm) into a 20 ml volumetric flask containing solvent and diluted to volume with solvent and mixed.

Preparation of Test solution: Weighed accurately about 100 mg of test sample into a 10 ml volumetric flask, dissolve it and diluted to the volume with solvent and mixed.

Preparation of Blend solution: Weighed accurately about 100 mg of test sample into a 10 ml volumetric flask and 1.2 ml each of MPTS and HAPTRC0$_2$, HAPTRC0$_3$, HAPTRC0$_4$ standard stock solutions (100ppm) shake well and diluted to the volume with solvent and mixed.

Procedure: Inject the blank solution and conclude the interference due to blank at the retention time of MPTS. Inject individual standard solutions of MPTS, HAPTRC0$_2$, HAPTRC0$_3$, HAPTRC0$_4$ and APT at test concentration level and record the chromatograms. Inject blend solution containing MPTS, HAPTRC0$_2$, HAPTRC0$_3$, HAPTRC0$_4$ and at limit level and APT at test concentration level and record the chromatograms. Establish relative retention time (RRT) for MPTS with respect to the APT retention time obtained from the blend solution.

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RESULTS AND DISCUSSION

Specificty was conducted by spiking MPTS along with H-APTRC0$_1$, H-APTRC0$_2$, H-APTRC0$_3$ respectively. There is no interference due to blank at the retention time of MPTS resolved from each other and from known impurities and APT (Fig-1).

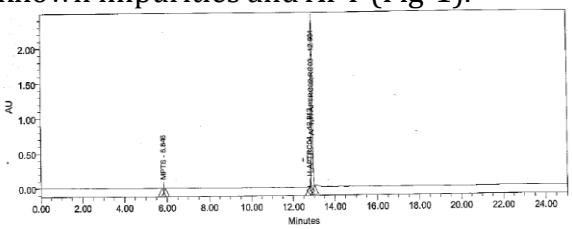

Fig- 1 Specificity Chromatogram

Limits of Detection for MPTS have been established. LOD solution was prepared so as to obtain the S/N ratio is in between 3 to 5 for MPTS the results are given in fig-2 and table-1.

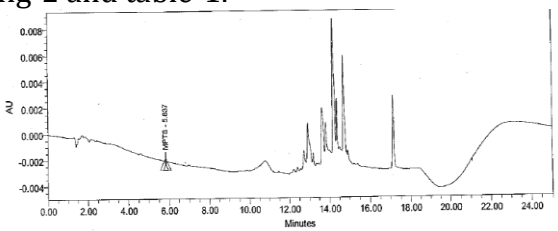

Fig-2 LOD Chromatogram

Table-1 Results of LOD

Name of the Compound	Conc. w.r.to. Test (ppm)	S/N Ratio
MPTS	1.33	4.7

Limits of Quantitation for MPTS have been established. Based on the concentration obtained from LOD, the LOQ solution was prepared (3 times to LOD concentration) so as to obtain the signal to noise ratios are in between 10 to 15 for MPTS, and the results are given in table-2 and fig-3.

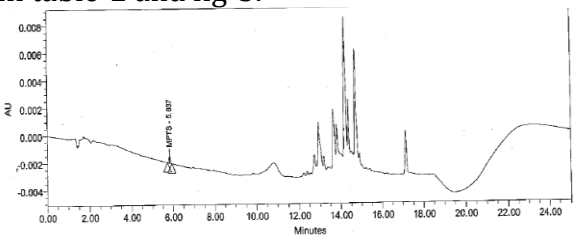

Fig-3 LOQ Chromatogram

Table-1 Results of LOQ

Name of the Compound	Conc. w.r.to. Test (ppm)	S/N Ratio
MPTS	4.0	12.4

Linearity study was conducted for MPTS and the range from LOQ level to 150% Specification as per the procedure mentioned in the protocol. Linearity graphs were obtained for MPTS in the range of LOQ 50% to 150% of specification. The results are given in table-3 and fig-4

Table-3 Results of MPTS Linearity Study

S.No	Conc (ppm)	Avg Peak Area
1	4.00	2185.0
2	6.00	2883.0
3	9.00	4613.5
4	12.00	6208.0
5	15.00	7672.5
6	18.00	9146.5
CC	0.9992	

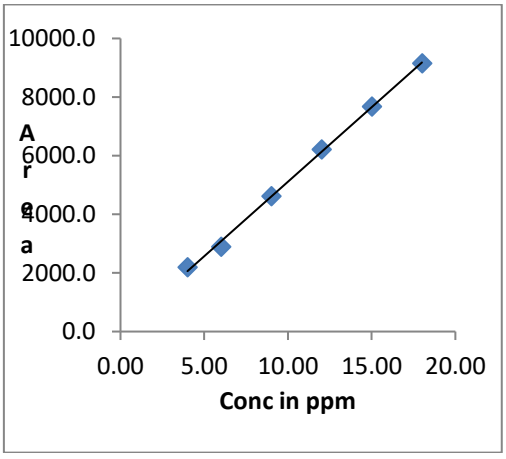

Fig-4 Linearity Graph

Sample-1 was analyzed three times (from three individual preparations) for accuracy Studies by spiking MPTS at LOQ level to it and evaluated the %

recoveries of MPTS at LOQ solution in Aprepitant. Results of accuracy at LOQ are given in table-4.

Table-4 Accuracy at LOQ Results

S. No.	Preparation	% Recovery of MPTS
1	Preparation-1	94.7
2	Preparation-2	96.8
3	Preparation-3	95.9

CONCLUSION

Above Observations from the present study indicate that the UPLC method meets the acceptance criteria for all the parameters selected for quantitation Study. Hence, the method is suitable for the determination of Methyl Para toluene Sulphonate in Aprepitant. Batch Analysis of Aprepitant (APT) sample demonstrates the absence of MPTS.

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