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A quality evaluation strategy for multi-sourced active pharmaceutical ingredient (API) starting materials

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Abstract

Establishing appropriate impurity specifications for active pharmaceutical ingredient (API) starting materials is an important component of the commercialization and registration of an API. Multiple sources and routes of manufacture of starting materials and the capability of the API synthetic process for tolerating impurities introduced with starting materials must be understood. A strategy for purity method development and use test evaluation of starting materials to aid in establishing quality requirements is described. Phenyl methyl amino propanol (PMAP), a starting material that may be used for fluoxetine hydrochloride and atomoxetine hydrochloride, is used to illustrate the quality evaluation strategy. Knowledge of actual and potential synthetic routes was used to predict potential impurities and guide purity method development. Multiple analytical methods that were semi-orthogonal in the nature of impurity retention (ion-pairing, ion interaction and hydrophilic interaction chromatographic modes) along with use tests were investigated.

Keywords: Liquid chromatography; API starting material; Ion-pairing; Quality by design; Impurity profiling; Perchlorate; Use test; Propinquity; Specifications; LC–MS

1. Introduction

Controlling the quality of starting materials used to prepare active pharmaceutical ingredients (APIs) is a critical part of ensuring the ultimate quality of the API itself. An API starting material is defined as a compound used in the synthetic sequence that contains a significant structural fragment of the API [1]. Recently, the designation of API starting materials has received much attention, in part due to the recent draft guidance provided by the FDA [2]. A key consideration for starting material designation resides in the analytical control strategy used for quality assessment. This is further emphasized in an industry position paper stating that specifications should be set to ensure appropriate control over downstream processing and drug substance quality [3]. The impurity profile should be developed with appropriate and discriminating analytical methods and include an assessment of actual and potential impurities based on the chemistry leading to that material [4,5]. Nevertheless, it is necessary to provide adequate confidence that the quality of the API starting material will be sufficient to produce API that meets its specifications. This is particularly important in terms of impurities that originate with the starting material and can carry through directly or can participate in the reaction chemistry to produce significant impurities in the API. A robust starting material quality evaluation strategy adds to the overall control of the quality of the resulting API and reduces the concerns that may be related to the propinquity of starting materials through quality by design rather than by testing alone.

Starting materials, by definition, can be purchased from external suppliers or produced by the firm that also manufactures the API. In addition, compliance to Good Manufacturing Practice guidelines is not required for production of compounds designated as API starting materials. It is possible and often likely that different synthetic routes may be used by different suppliers to produce the starting material and these routes may produce different impurities. In some cases, the synthetic route may not be disclosed to the API producer. These considerations dictate that a thorough investigation of impurities in starting materials be conducted. This investigation includes, but is not limited to method development, an intentional search for

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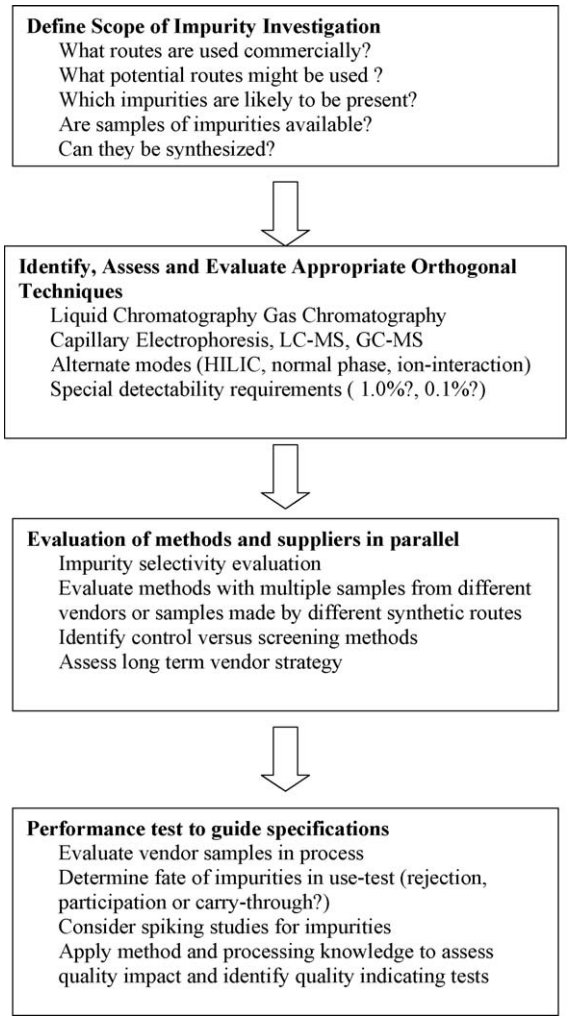

Fig. 1. A general quality evaluation strategy for starting materials.

potential impurities, the identification of significant unknown impurities and assessment of impurity impact on API quality. Results of such an investigation are used to set specifications for the starting material that will assure suitability for use in API production.

This paper describes a quality evaluation strategy for API starting materials. A general outline of the strategy is provided in Fig. 1 and the paper will focus on the application of the strategy to illustrate how it can be used to develop a robust understanding of starting material quality. Phenyl methyl amino propanol ((±)3-methylamino-1-phenylpropanol, PMAP), a starting material that may be used in the synthesis of fluoxetine hydrochloride [6] and atomoxetine hydrochloride [7], is used as an example (Fig. 2). Knowledge of actual and potential synthetic routes was used to predict potential impurities and guide purity method development. Multiple analytical methods were used to screen material from several vendors and results used to choose the appropriate method for quality control. Results from sample analysis and use tests in the synthetic process were used to determine the appropriate controls necessary to consistently deliver high quality API.

2. Experimental

2.1. Equipment

Chromatographic analyses were performed on Agilent Technologies G1100 systems (Waldbronn, Germany) equipped with a vacuum degasser, quaternary pump, refrigerated autosampler, thermostated oven device and a variable wavelength UV detector or on a Hitachi Model L-6200A pump (Naperville, IL),with an Alcott model 728 autoinjector (Norcross, GA), Valco injection valve (Houston, TX), and Applied Biosystems variable wavelength UV detector, model 757 (Ramsey, NJ). The chromatographic data were acquired and analyzed using Millenium^{32} software, Version 3.2 (Waters Corporation, Milford, MA) or on an in-house-modified HP1000 data acquisition system. The voltage units plotted in the figure chromatograms are propor-

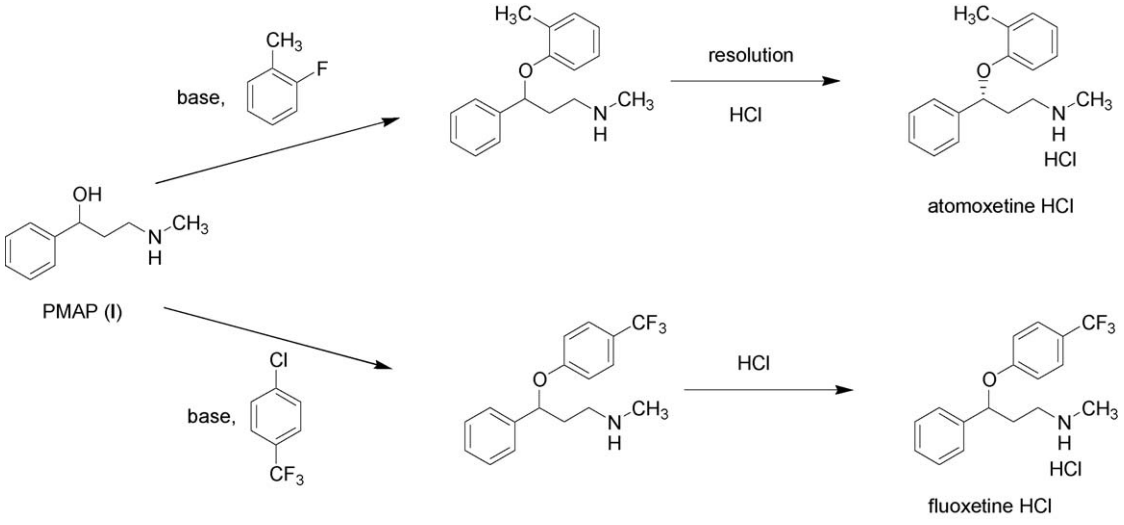

Fig. 2. Potential routes of manufacture for fluoxetine [6] and atomoxetine [7] using a common API starting material (PMAP).

tional to absorbance. For GC-MS, the samples were evaluated on a Hewlett-Packard 6890 GC and 5973 Mass Selective Detector in electron ionization mode. For LC–MS, the samples were analyzed on a Waters Alliance 2690 and Waters PDA 996 and Micromass LCT Time-of-Flight mass spectrometer, using positive ion mode with electrospray.

2.2. Chromatographic mobile phases and gradient conditions

2.2.1. Hydrophilic Interaction (HILIC)

Isocratic separations were carried out on a 25 cm × 4.6 mm i.d. Zorbax NH_2, 5 μm particle size column with a mobile phase consisting of 15% 10 mM phosphoric acid adjusted to pH 6.1, 85% acetonitrile. The flow rate was 1.0 ml/min with UV detection at 215 nm.

2.2.2. Ion-pairing

Isocratic separations were carried out on a 15 cm × 4.6 mm i.d. Zorbax Eclipse XDB-C8, 3.5 μm particle size column using a mixed aqueous/organic mobile phase consisting of 80% 25 mM *o*-phosphoric acid, pH 2.5, 35 mM octanesulfonic acid; 20% *n*-propanol. Isocratic conditions for atomoxetine samples were carried out using a mixed aqueous/organic mobile phase consisting of 73% 25 mM *o*-phosphoric acid, pH 2.5, 25 mM octanesulfonic acid; 27% *n*-propanol with a column temperature of 40 °C. The flow rate was 1.0 ml/min with UV detection at 215 nm for both sets of conditions.

2.2.3. Ion-interaction

Separations were carried out on a 25 cm × 4.6 mm i.d. Zorbax RX-C8, 5 μm column with UV detection at 215 nm. The aqueous component of the mobile phase consisted of 25 mM sodium perchlorate and 25 mM potassium phosphate, pH 2.7. The gradient conditions started with an initial hold for 5 min at 15% acetonitrile/85% buffer, were ramped to 60% acetonitrile/40% buffer over 10 min and held at 60% acetonitrile/40% buffer for 5 min. The HPLC system was allowed to re-equilibrate to initial conditions for at least 9 min before the next injection.

2.2.4. Gas chromatography–mass spectrometry (GC–MS)

Samples were prepared at 100-mg/ml concentration in methanol. A DB-5 capillary column (30 m × 0.32 mm × 1 μm) was used with a 25:1 split ratio. The column was held at 100 °C for 3 min followed by a 10 °C/min ramp to 275 °C, with a final hold time of 5 min to ensure complete elution of components of interest. The average velocity used was 39 cm/s. Electron ionization mode was used for detection with source and quadrupole temperatures of 150 and 230 °C. The mass range covered for GC experiments was *m*/*z* 35–550.

2.2.5. Liquid chromatography–mass spectrometry (LC–MS)

The chromatography was performed using a 0.1% TFA (v/v) /acetonitrile gradient on a Zorbax SB-C8, 25 cm × 4.6 mm i.d., 5 μm particle size column, at 25 °C at a flow rate of 1.5 ml/min. The gradient conditions started with an initial hold for 5 min at 15% acetonitrile/85% aqueous, were ramped to 60% acetonitrile over 10 min and held at 60% acetonitrile for 5 min. A 20 μl injection volume was used. The mass range investigated by LC–MS experiments was *m*/*z* 100–1200.

2.3. Materials

Aqueous portions of the mobile phases were prepared in deionized water (18.2 MΩ) from a Millipore Milli-Q Plus water purification system (Millipore, Billerica, MA). Aqueous phosphate systems were prepared from *o*-phosphoric acid (85%) unless otherwise specified. Potassium phosphate monobasic (EM Science, Darmstadt, Germany) and *o*-phosphoric acid (85%, w/w, HPLC grade) were purchased from Fisher Chemicals (Fair Lawn, NJ). Adjustments to the pH of the aqueous phase were achieved by addition of 5 M potassium hydroxide (reagent grade, Sigma–Aldrich). HPLC grade (Omnisolv) solvents *n*-propanol (*n*-propyl alcohol), acetonitrile, and methanol were obtained from EM Science (Gibbstown, NJ). A.C.S. reagent grade, trifluoroacetic acid (TFA), 99% and sodium perchlorate were purchased and used as received from Aldrich (Milwaukee, WI). Octanesulfonic acid sodium salt monohydrate (>98%) was purchased from Fluka. Impurity samples and authentic reaction products from proposed synthetic routes that were not commercially available were supplied by the Chemical Product Research and Development laboratories of Eli Lilly and Company. Most PMAP samples were produced as described in the literature [6]. The Zorbax Eclipse, XDB C-8 (15 cm × 4.6 mm i.d., 3.5 μm), Zorbax RX-C8 (25 cm × 4.6 mm i.d., 5 μm) and Zorbax NH2 (25 cm, 4.6 mm i.d., 5 μm) columns were purchased from Agilent (Waldbronn, Germany).

3. Results and discussion

3.1. Potential impurities

Methods used to screen early development samples need to be capable of detecting likely impurities. The scope of the impurity investigation can be determined by considering synthetic routes that may be used to produce the compound. For example, Wirth et al. [6] described six potential commercial routes that may be used to synthesize PMAP, a potential intermediate in the synthesis of fluoxetine or atomoxetine (Fig. 2), and Sheldon and Downar [8] evaluated three potential synthetic routes for the synthesis of orbofiban. The benefits of evaluating multiple synthetic routes to manufacture the starting materials at the initiation of method development is that potential impurities of interest can be used to assist in defining the scope of development and minimize the re-development due to new impurities found as additional vendor experience is gained. Using this approach for PMAP, potential impurities that may be predicted from the routes in Fig. 3 are given in Fig. 4. These potential impurities originate from a wide array of reactions, each with the potential for a unique impurity profile and thus represent a broad scope for defining the capability of the analytical method.

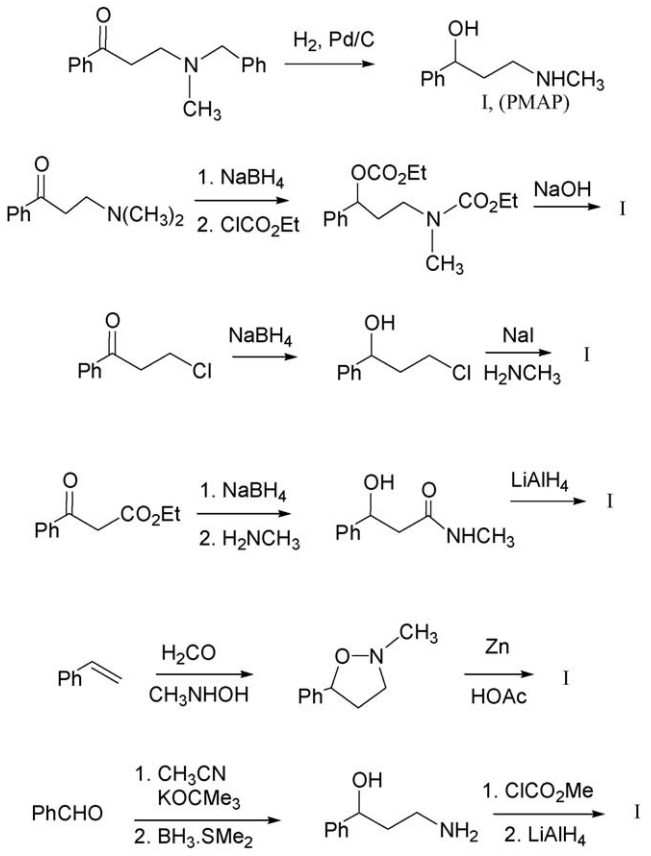

Fig. 3. Synthetic routes to PMAP [6].

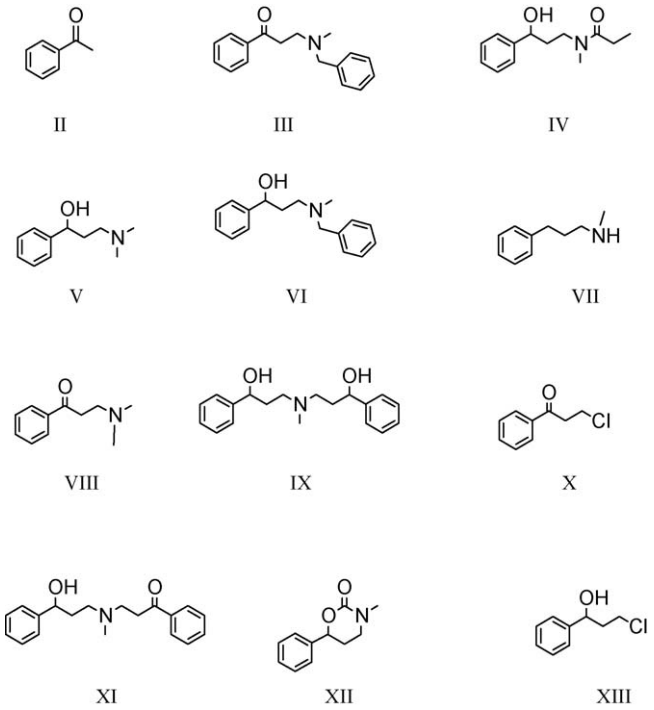

Fig. 4. Potential PMAP impurities.

3.2. Method development

Consideration of the properties of potential impurities shown in Fig. 4 was used to guide method development for PMAP purity determination. Consistent with the strategy outlined in Fig. 1, it is important to consider multiple analytical techniques that could be investigated, but to be selective in determining which techniques to actually investigate. For example, although several impurities in the manufacture of PMAP are amenable to gas chromatographic (GC) analysis, some compounds such as the diols, undergo thermal decomposition making GC inappropriate for general screening. Thus, while useful for orthogonal information, GC would not be a long-term approach and minimal development effort should be invested in the approach. Many of the compounds in Fig. 4 are polar in nature, requiring high performance liquid chromatographic methods that will provide adequate retention. Options for retaining polar compounds include reversed-phase HPLC with highly aqueous mobile phases, use of a basic mobile phase with base stable columns, addition of ion-pairing (alkyl sulfonates or sulfates) or ion interaction agents (perchlorate) [9–11] or use of alternate modes such as hydrophilic interaction chromatography (HILIC) [12–14]. These modes provide a degree of orthogonality to the overall analytical investigation and may provide unique information that might otherwise be overlooked with narrow scope chromatographic modes [15]. Given a number of appropriate options, some or all of these should be investigated and later evaluated in terms of operational or selectivity advantages they provide when an implementation decision needs to be made. Specifically, separation using base stable columns has been investigated for PMAP. Adequate retention of PMAP was obtained under basic conditions on a Waters Xterra MS C-18 column, however selectivity for the impurities in PMAP was not pursued as alternative conditions offered advantages in terms of operational efficiency. Capillary electrophoresis could also be used, although complexation methods such as micellar electrokinetic chromatography would be necessary to ensure separation of neutral impurities that may arise from multiple suppliers or multiple routes of synthesis.

The ability to identify unknown impurities with a method compatible with either LC–MS or GC–MS method during development studies can be quite beneficial for impurity fate and tracking and thus conditions were developed for this purpose. Long term implementation of either method for the example starting material was not chosen due to technical or end-use requirements, but the LC–MS method could be utilized if necessary.

In addition, a final consideration is the intent of the method: vendor screening, control, or both. It is often beneficial to have more than one approach in early evaluations of starting materials and once the appropriate level of control is defined, usually through specifications, a validated method for control and long-term use can be implemented. Using the information from the assessment of potential impurities and analytical tools, the focus for method development was chosen to include reversed-phase HPLC in the ion-pairing, ion-interaction and HILIC modes, as well as to parallel the work with an LC method compatible with

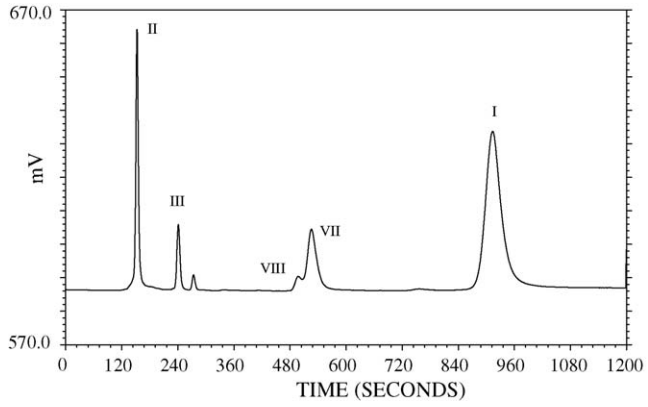

Fig. 5. HILIC conditions on amino column. The structures corresponding to impurities II, III, VII and VIII can be found in Fig. 4.

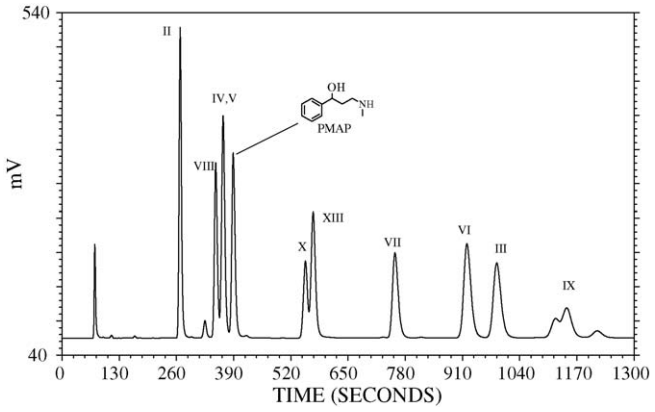

Fig. 7. Ion-pairing separation of PMAP and potential impurities. The structures corresponding to the impurities in the chromatogram can be found in Fig. 4.

MS detection. The information generated from these investigations was used to identify a final set of conditions to advance to the next stage of evaluation.

The range of polarities of PMAP and potential impurities in Fig. 4 represents a challenge to reversed-phase HPLC methods in that sufficient retention of PMAP is required, but this often comes as a tradeoff for either peak shape or run time due to retention of less polar compounds such as III in Fig. 4. Stationary phases designed for polar compounds provided little retention of PMAP even with highly aqueous mobile phases so alternative approaches were pursued. An amino column used under HILIC conditions provided significant retention for PMAP and separated several impurities (Fig. 5). However, the column was overloaded at PMAP concentrations sufficient for impurity determinations (2 mg/ml) resulting in poor peak shapes. Thus, while HILIC achieves the goal of retention and demonstrates some selectivity for PMAP impurities, the utility of this approach as a control strategy was limited.

Aqueous perchlorate has been reported as a useful mobile phase additive for the retention of polar basic compounds [9]. Fig. 6 shows the selectivity obtained for PMAP and related substances using a low pH perchlorate-containing mobile phase.

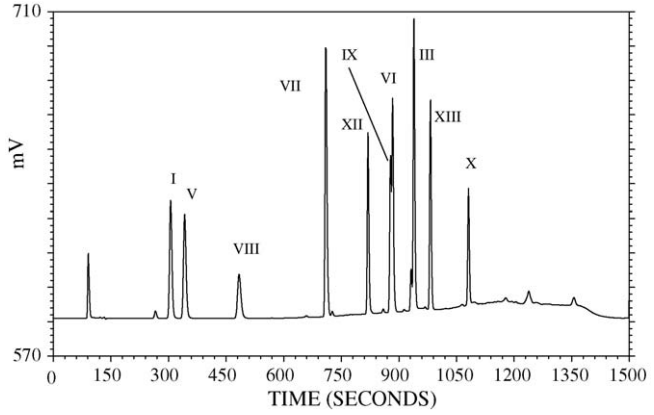

Fig. 6. Ion interaction separation of PMAP impurities of interest. The structures corresponding to the impurities in the chromatogram can be found in Figs. 2 and 4.

An acetonitrile gradient was employed to elute less polar compounds. With this system, PMAP was well retained and good selectivity was achieved for potential impurities. Thus, a perchlorate system could be considered as an option for PMAP and indeed was advanced to the next stages of method development.

Methods used for the APIs also provided options for the analysis of PMAP and from a general strategy approach are worth consideration for starting material methods. This is especially important when the starting material is similar in structure to the API (see Fig. 2) as is the case for PMAP. The conditions that were suitable for the analysis of fluoxetine and atomoxetine were considered as starting points for the analysis of PMAP. Neither method would meet the needs for the control of starting material quality due to a lack of significant retention of PMAP and/or likely impurities. This is not unexpected as the intent of the methods is quite different; control of API purity versus control of a starting material. However, a modification to the ion-pairing system used for analysis of atomoxetine hydrochloride appeared promising and was investigated for PMAP. The API conditions were readily adapted for the starting material evaluation based upon the knowledge gained during atomoxetine API impurity method development where PMAP was an impurity rather than the main component. Adequate separation of impurities was obtained using isocratic conditions (Fig. 7). The two potential impurities eluting just before PMAP would be detected even at high PMAP concentrations.

The ability of this method to detect impurities in PMAP from different synthetic routes and/or different vendors is demonstrated in Fig. 8. It is clear from Fig. 8 that different synthetic routes to manufacture PMAP produced qualitatively and quantitatively different impurity profiles. However, the ability to directly identify impurities in an ion-pairing medium can be challenging, and thus it is important to have alternative conditions that are compatible with MS for direct identification. This is especially important for starting materials because while it is possible to predict potential impurities to provide robust methodologies, the probability for impurities to occur that were not captured in the assessment is still quite high.

The benefit of an MS compatible LC method was demonstrated when examining samples for the presence of impurity III.

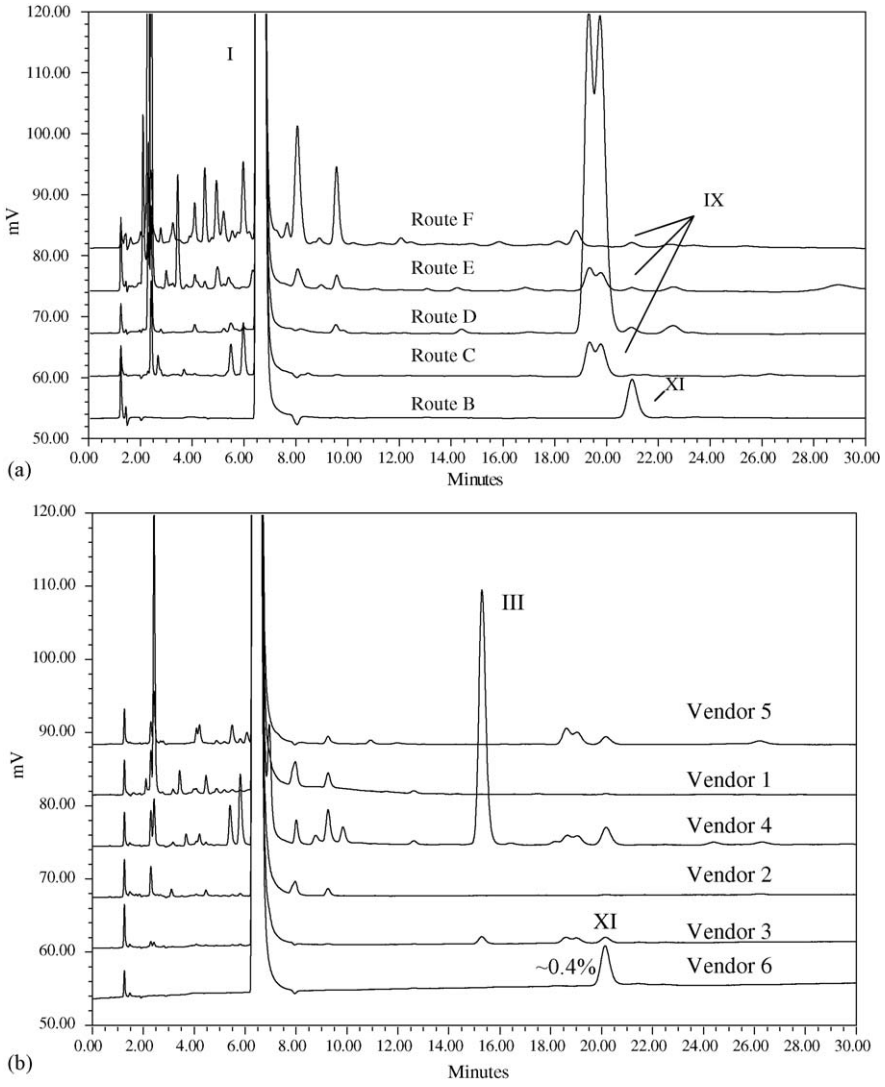

Fig. 8. Chromatographic analysis using the ion-pair methodology for (a) different synthetic routes (b) different vendors using the ion-pair method. The structures for the impurities identified in the chromatograms can be found in Fig. 4.

While solutions containing III alone showed a single peak with a retention time well separated from that of PMAP, compound III was not recovered when added to a concentrated PMAP sample solution. Instead, two other peaks were observed as shown in Fig. 9. Molecular weights for these compounds were determined using a reversed-phase gradient system using a volatile mobile phase consisting of TFA and acetonitrile. This information led to identification of the compounds as XI and XV, and the proposal that they arise from retro-Michael decomposition of III into phenyl vinyl ketone and XV, and Michael addition of PMAP to phenyl vinyl ketone (Fig. 10). This reaction occurred when III was in solution with a large excess of PMAP. Knowledge of this phenomenon explained the lack of recovery of III when added to PMAP sample solutions. From an analytical perspective, the identification combined with an understanding of what was occurring in the analysis allowed analytical controls to be implemented to detect and quantitate III when actually present in samples of PMAP. Specifically, sample storage conditions and duration were investigated as a means of controlling the

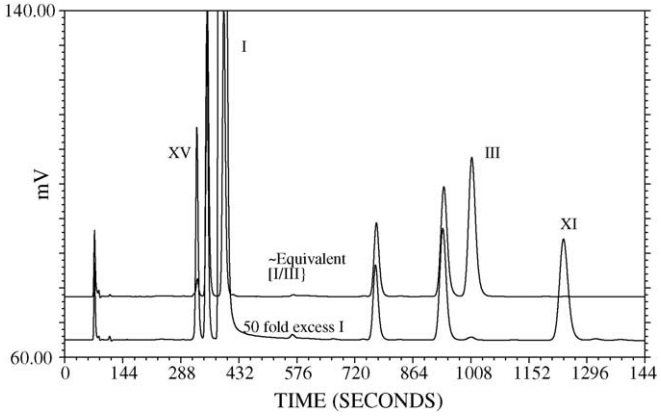

Fig. 9. Chromatograms obtained with the ion-pairing system demonstrating two new impurities formed (XI, XV) and the disappearance of III when added to a high concentration of I (PMAP). The structures corresponding to the impurities in the chromatogram can be found in Fig. 10.

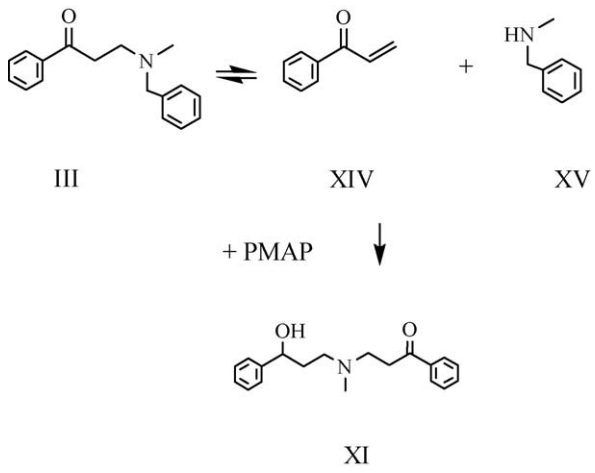

Fig. 10. Michael/Retro–Michael reactions proposed for III in the presence of a large excess of I (PMAP).

kinetics and extent of the reaction, resulting in the use of refrigerated sample storage for a maximum of 10 h. The knowledge of the presence of III in authentic samples of PMAP affords the manufacturing operation or vendor the ability to better refine process control as III would not typically be expected. If III were present, it would be resolved and accurately quantitated with the controlled assay conditions. The presence of III may indicate that either a process upset had occurred or additional controls should be added to maintain the quality of the starting material.

3.3. Vendor qualification and evaluations

Demonstration that a vendor's starting material is appropriate for commercial manufacturing of an API is a commonly understood expectation [1–3]. However, there is less guidance with regard to the extent or depth that these evaluations should be performed in order to develop and define a scientific and risk based rationale in support of the API starting material justification and control strategy. As part of the overall strategy outlined in Fig. 1, PMAP samples from six manufacturers were obtained and evaluated using the two methods (ion-interaction and ion-pairing) that appeared to offer the best selectivity from initial stages of development. Conceptually, the methods worked quite well with the postulated impurities; however the specific route a vendor uses is not always disclosed. Thus, the use of two technologies for the assessment affords the opportunity to gain information about (a) actual commercial routes employed and the accuracy of the predicted impurities that are observed (b) robustness and orthogonality of the methods under consideration and (c) preliminary assessment as to the levels of impurities that may enter the API process through the PMAP starting material. In parallel with the vendor screening, several of these samples were analyzed by both LC–MS and GC–MS. The mass spectrometric approaches supplemented the knowledge from the ion-pairing and ion-interaction conditions as well as provided mass information on impurities that were not previously identified.

Fig. 8 shows an example of the results from the use of the ion-pairing conditions. A comparison of the two overlays in Fig. 8a and b, reveals the benefits of the initial route evaluation for method development as well as insight into the robustness of the method. Clearly, the method is capable of distinguishing differences in the quality of PMAP. In addition, several impurities that were included in initial method development, were present in vendor samples (Fig. 8b). However, it is also clear that several impurities are present in the vendor samples that were not included initially, but are either fully or partially resolved from the main peak. The ion-interaction conditions (data not shown), while exhibiting different retention characteristics provided similar results in terms of clear differences in quality among the vendors. The different selectivity afforded by the two methods provided confidence that significant impurities in the samples were detected. Several proposed or potential impurities in vendor samples were confirmed using the LC–MS or GC–MS methods and mass assignments or tentative structures were made to any "new" impurities. This multiple vendor approach, combined with LC or GC mass spectrometric identification helps support the overall knowledge and robustness of the control strategy for the starting material.

A key aspect of the strategy involves the development of methods to evaluate or screen the proposed qualities of commercially supplied material. An additional parameter that should be considered during these evaluations is the long-term use of the method conditions being developed. It is quite beneficial to have multiple methods, including LC–MS compatible conditions to screen vendors. In the conditions evaluated for PMAP, a choice was made between the two sets of conditions that advanced through the screening stage. Both sets of conditions were adequate for their intended use in terms of both selectivity and sensitivity, but only one was advanced through validation studies. The isocratic ion-pair method was viewed as a stronger candidate for implementation in the control laboratory based upon the ease of operation and similarity of the conditions to the API method.

3.4. Suitability for intended use

A critical aspect of starting material evaluation is to determine how samples of varying quality perform in the desired synthesis, i.e., a use test. This provides information regarding impurity carry-over and fate and can be used to scientifically justify the level of impurity control required for the API synthesis. Examination of the range of impurity profiles of PMAP that can be commercially obtained in Fig. 8, could lead to several impurity control strategies for the starting material. One might suggest that API-like impurity acceptance criteria (no impurity >0.1%) be used based upon propinquity to the API (see Fig. 2). An approach like this can be employed, and if necessary, is quite effective. However, caution should be used with this strategy if it relies only upon impurity profiling of vendors, as it may be unnecessary and result in over-stringent controls. The approach detailed in this paper incorporates information from not only impurity profiles, but other quality indicating parameters that may be important (assay, water) in addition to the evaluation

Table 1
Vendor trial results

Vendor	Water (KF, %)	Assay (PMAP)	Impurities (PMAP, %)	Impurities in atomoxetine (%)	Difference from control yield (%)
1	0.13	98.5	0.79	0.08	−1
1	1.14	88.9	11.9	1.95	−11
2	0.05	99.0	0.07	0.06	−2
2	0.04	99.4	0.09	0.13	−1
3	0.05	100.4	0.69	0.14	−1
3	0.04	99.9	0.63	0.21	−2
4	0.33	95.3	2.10	0.28	−7
4	0.64	87.8	5.75	0.35	−11
5	0.18	98.7	0.72	0.16	−4
5	0.17	97.8	0.81	0.19	−4
6	0.03	99.6	0.45	0.08	0

of samples in their intended use to develop acceptance criteria. This approach includes both the quality and yield of the reaction product as important factors in the evaluation and provides a firm relationship between what quality can be supplied, what is needed for the intended quality of the product and what, if any, impurities are indeed critical and need to be controlled. Fig. 11 shows how this is applied to PMAP, showing impurity profiles of atomoxetine (the reaction product from Fig. 2) prepared using PMAP from different vendors. The API method was capable of separating and detecting potential reaction products between 2-fluorotoluene and several of the impurities given in Fig. 4. No impact on drug substance quality from impurities present in the vendor samples was found. Thus, the need to apply tight controls to the vendors in this example is not critical to the quality of the API produced. Since the method used to evaluate the drug substance trial reaction samples was isocratic, the reaction products were also examined with stronger solvent conditions to check for the presence of any new, unanticipated non-polar impurities. LC–MS or GC–MS tools also could have been used to confirm the absence of new impurities derived from the starting material and further supplement the knowledge of the starting material requirements.

A summary of PMAP vendor sample evaluation using the ion-pairing method for quality assessment and the yield and quality of the trial reaction product is shown in Table 1. Six vendors, using a variety of synthetic routes as evidenced by their impurity profiles in Fig. 8 were evaluated, with several vendors submitting multiple samples. Several aspects of starting material evaluation are apparent. Although vendor 1 provided one sample that was acceptable, another sample from the same company was very high in impurities and produced unacceptable quality product. Vendors 2, 3 and 5 had consistent quality PMAP that produced high quality atomoxetine in acceptable yield. PMAP from vendor 4 contained high levels of impurities compared to other vendors but these impurities did not have a significant impact on impurities in atomoxetine. Thus, the process may be robust with regard to incoming impurities in PMAP. This also highlights the need to consider and understand the level, fate and nature of impurities in setting appropriate specifications. Samples from vendor 4 did show a yield decrease in the trial reaction, causing this vendor to not be considered for future purchases. The results from the vendor quality and trial reactions helped provide rationale for establishing scientifically justified impurity control limits on PMAP quality. It is clear from Table 1 that the synthetic route has robust impurity rejection capability and the main impact of the starting material quality is in the overall reaction yield.

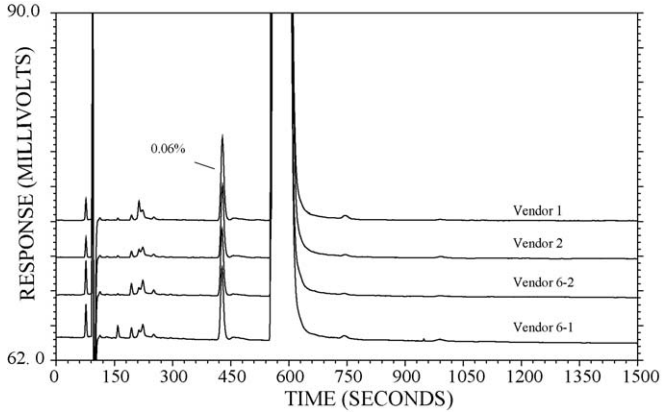

Fig. 11. Atomoxetine impurity profiles using different suppliers of PMAP. Vendor 6 submitted two samples of PMAP that were evaluated in the use test and thus these are identified as 6-1 and 6-2.

4. Conclusions

Method development for the determination of impurities in API starting materials should take into account the various synthetic routes that may be used to produce the starting material. Synthesis of potential impurities in the starting material is extremely valuable for use in method development and is essential when the starting material is similar in structure to the API or proximate to it in the synthetic sequence. It may be necessary to maintain multiple methods during the initial phases of starting material characterization and evaluation. Use testing is necessary to determine the impact of starting material quality on the quality and yield of the API and in addition demonstrates that the quality of the API as derived from the starting material is both controlled and well understood. Qualification of new suppliers should also include a downstream assessment to ensure that new impurities are not present and where appropriate, impurity spiking studies may be employed to further confirm

rejection or define acceptance limits. In this paper, there is significant focus on the application of a strategy for multi-sourced or multi-route starting materials, with PMAP used as an example to elucidate the strategy. However, the approach could also be applied to situations where the material is supplied in-house or by a single known synthetic route, as part of the development of a robust impurity control strategy. A strategy that incorporates: (a) appropriate and discriminating analytical methods at the starting material and downstream product(s), (b) understanding of known and potential impurities, as well as their fate or impurity carry-over and (c) evaluation in the synthesis of the API can provide a strong scientific rationale to establish appropriate specifications for the starting material. Furthermore, this level of understanding and control is expected as the proximity to the API increases and should be provided as support for an API starting material designation. This information can also be communicated to vendors for help in improving their production processes and insuring consistent quality starting material from multiple sources delivered to the API manufacturer. The use of process knowledge combined with discriminating analytical methodology for starting material evaluations, can produce a thorough understanding of the quality requirements for the starting material and aligns with recent expectations of quality by design.

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