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A quality by design approach to impurity method development for atomoxetine hydrochloride (LY139603)

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Abstract

The development of an ion-pairing HPLC method and associated system suitability parameters for the analysis of atomoxetine hydrochloride (LY139603 HCl) using a quality by design approach is described. Potential method conditions were evaluated for their ability to meet design requirements and statistically designed experiments were used to optimize conditions and demonstrate method robustness for the separation of atomoxetine and impurities. The separation of two early eluting impurities, phenyl methylaminopropanol (PMAP (±)3-methylamino-1-phenylpropanol) and mandelic acid is correlated to the separation of other impurities that elute near the main sample component and the resolution of this peak pair is used as a system suitability test without the need for impurity reference standards.

Keywords: Liquid chromatography; Ion-pairing; Quality by design; System suitability; Column equivalence; *In situ* degradation; Atomoxetine

1. Introduction

Quality by design (QbD) is a key principle that has gained much discussion since its initiation as part of the U.S. Food and Drug Administration's vision for the 21st century cGMPs and the International Conference on Harmonisation (ICH) guidance on pharmaceutical development [1,2]. The fundamental principle of the initiative is to demonstrate both understanding and control of pharmaceutical processes to deliver high quality pharmaceutical products while affording opportunities for continuous improvement. While it is clear that the initiative is primarily intended for pharmaceutical product development, its use in the development of an integrated control strategy that involves analytical technology and methods should not be underestimated. In fact, many of the terms used in the QbD initiative are very familiar to analytical chemists when put into the context of method development activities for new pharmaceutical ingredients.

Analytical methods used for the analysis of active pharmaceutical ingredients (API) and drug products are an integral part of the quality by design concept that is outlined in ICH Guideline Q8 for pharmaceutical development [2]. It is important that methods used for analysis meet their intended purpose similar to the product requirements for a clinical dosage form. It is also clear that in order to develop robust, stability indicating analytical methods, a solid set of design requirements must be established to ensure that the method meets its intended use. Methods used for impurity analysis need to be capable of detecting both process and degradation related impurities. Impurities arising from starting materials and/or reaction by-products, whether they carry through the synthetic process unaltered or participate in chemical reactions, must be part of the design requirements for the appropriate impurity method. This type of holistic consideration of impurity nature and fate becomes a key piece of the overall analytical control strategy. Intentional application of quality by design principles to the control strategy can result in a paradigm shift from quality through analytical testing to one where the analytical method verifies that the API or drug product process has been executed as designed.

Design requirements, however, are just one piece of analytical method development activities that mirror the 21st Century GMP initiatives. Analytical chemists are quite familiar with design space or a combination of parameters, within which, the process

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(or method) delivers the desired outcome. The deliberate evaluation of the range around a specified set of conditions where the desired property is intended to be measured is often referred to as the evaluation of the robustness of the method. Robust methods, given a defined region, need very little intervention to remain suitable for the intended use, whereas sensitive methods require stringent controls (due to limited design space) on method parameters in order to operate as intended. The compendia have viewed design space as the acceptability of changes in method conditions within outlined guidances [3]. Method performance within this variation is confirmed with system suitability requirements. In a way, system suitability can be viewed as another element of quality by design for analytical chemists, when applied appropriately, as it helps to identify failure modes and can prevent the generation of erroneous results.

In this paper, the development of the impurity method for atomoxetine hydrochloride is described in terms of quality by design concepts. Considerations for method development or design are discussed in terms of potential impurities, actual impurities and the linkage between the analytical method and the overall process control strategy. Statistically designed experiments were used to identify the optimal operating conditions as well as evaluate the range of several important method parameters. Knowledge from method development and validation experiments proved quite beneficial in the establishment of a correlated peak system suitability approach that affords control and demonstration of the acceptability of the method each time it is run without the need for impurity standards.

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, thermostatted oven device and a variable wavelength UV detector. The chromatographic data were acquired and analyzed using Millenium^{32} software, version 3.2 (Waters Corporation, Milford, MA), Empower (version 5.00) or on an in-house-modified HP1000 data acquisition system. The voltage units plotted in the chromatograms are proportional to absorbance. Statistically designed experiments were designed and analyzed using JMP 5.1.1 (SAS Institute, Cary, NC).

2.2. Chromatographic mobile phases and sample preparation

2.2.1. 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 73% 25 mM *o*-phosphoric acid, pH 2.5, 25 mM octanesulfonic acid; and 27% *n*-propanol, with a column temperature of 40 °C unless otherwise indicated. The flow rate was 1.0 ml/min with UV detection at 215 nm. The mobile phase mixtures used in the robustness study were prepared as outlined in Table 1. Samples for the

Table 1
Fractional factorial design (FFD) to assess method robustness

Code	Buffer concentration (mM)	pH	Ion-pairing agent (mM)	*n*-Propanol (%)	Column temperature (°C)	Pressure (bar)	R_s (1–2)	R_s (3–4)	R_s (4–5)	Run time (min)	Tailing
+−−++	30	2.3	20	28	45	181	4.45	7.64	4.50	12.68	1.23
00000	25	2.5	25	27	40	192	6.49	8.88	5.17	16.80	1.21
+−−++	30	2.3	20	28	45	179	4.54	7.81	4.65	12.96	1.25
00000	25	2.5	25	27	40	199	6.95	8.56	4.97	19.43	1.21
−+−+−	20	2.7	20	28	35	218	5.88	8.22	4.89	15.42	1.23
++++	30	2.7	30	28	45	179	6.13	8.10	4.61	14.21	1.23
+−+−−	30	2.3	30	26	35	211	8.83	10.14	5.84	26.13	1.18
00000	25	2.5	25	27	40	200	6.83	8.48	4.92	19.04	1.21
00000	25	2.5	25	27	40	189	6.84	9.15	5.35	18.43	1.23
+−+−−	30	2.3	30	26	35	211	9.11	10.35	5.97	27.50	1.19
−+−+−	20	2.7	20	28	35	221	6.22	8.18	4.85	17.29	1.24
−+−−+	20	2.7	30	26	45	177	8.57	9.52	5.43	21.15	1.21
−−−−+	20	2.3	20	26	45	181	6.94	9.37	3.00	20.12	1.25
++−−−	30	2.7	20	26	35	214	7.36	9.62	5.78	24.81	1.21
++−−−	30	2.7	20	26	35	200	7.58	10.42	6.35	23.24	1.22
++++	30	2.7	30	28	45	187	5.85	7.72	4.37	13.57	1.21
−−++−	20	2.3	30	28	35	223	7.30	8.38	4.77	18.24	1.20
−−−−+	20	2.3	20	26	45	182	7.47	8.71	5.15	22.82	1.23
−++−+	20	2.7	30	26	45	181	8.74	8.87	5.03	23.35	1.21
−−++−	20	2.3	30	28	35	212	7.17	8.72	5.00	17.46	1.22