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Quality by Design in the development of hydrophilic interaction liquid chromatography method with gradient elution for the analysis of olanzapine

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ABSTRACT

This paper deals with the development of hydrophilic interaction liquid chromatography (HILIC) method with gradient elution, in accordance with Analytical Quality by Design (AQbD) methodology, for the first time. The method is developed for olanzapine and its seven related substances. Following step by step AQbD methodology, firstly as critical process parameters (CPPs) temperature, starting content of aqueous phase and duration of linear gradient are recognized, and as critical quality attributes (CQAs) separation criterion *S* of critical pairs of substances are investigated. Rechtschaffen design is used for the creation of models that describe the dependence between CPPs and CQAs. The design space that is obtained at the end is used for choosing the optimal conditions (set point). The method is fully validated at the end to verify the adequacy of the chosen optimal conditions and applied to real samples.

1. Introduction

Nowdays, in analysis of small polar molecules and substances with basic characteristics as very convenient hydrophilic interaction liquid chromatography (HILIC) is used. Advantages of HILIC over the most often used RP-HPLC in this particular analysis could be seen in better peak shape, in retention behavior of very polar substances and often shorter analysis time. As consequence, it could be noticed rising application of HILIC in pharmaceutical analysis [1]. Taking into account that in modern pharmaceutical analysis separation of complex analytical mixtures is demanded, gradient elution is very often employed. In difference from RP-HPLC method where gradient elution is well documented, there are no so many papers where gradient elution in HILIC is explained. This is probably related to complex separation process involved in HILIC separation. It is difficult to define the HILIC retention mechanism completely and accurately. It can be affected by ion-exchange, ion-repulsion, size-exclusion, ion-pairing or reversed phase mechanisms, and the solute distribution between the stationary and the mobile phase can be adsorption, partition or a combination of both effects, regardless of the previously mentioned mechanisms [2]. To understand the HILIC retention and separation, the characteristics of both analytes and stationary phases need to be taken into consideration [3]. Taking into account complexity of HILIC it is always challenging to develop new methods especially when gradient mode is used.

Searching the literature, several papers dealing with method development of gradient HILIC methods were found. Individual retention modeling was used for gradient optimization in some papers, by prediction of individual retention times using different theoretical models, as well as the empirical model proposed by Neue and Kuss [4,5]. Apart from that, the authors sometimes develop specific software packages in order to facilitate method development process, such as ACD/LC Simulator [6]. Another strategy described for HILIC method development was the usage of predictive elution window stretching and shifting for the automated method development process [7]. The main goal of all these researches is to find the easiest and most efficient approach to method development of a complex analytical method such as HILIC.

Talking about modern method development approaches and regulatory recommendations, it is necessary to mention Quality by Design (QbD) concept defined in detail in guidelines [8–10]. This approach if applied to the method development is called Analytical QbD (AQbD). It is becoming less of a recommendation and more of an obligation for the companies to develop analytical methods in this systematic and scientifically founded approach. Also,

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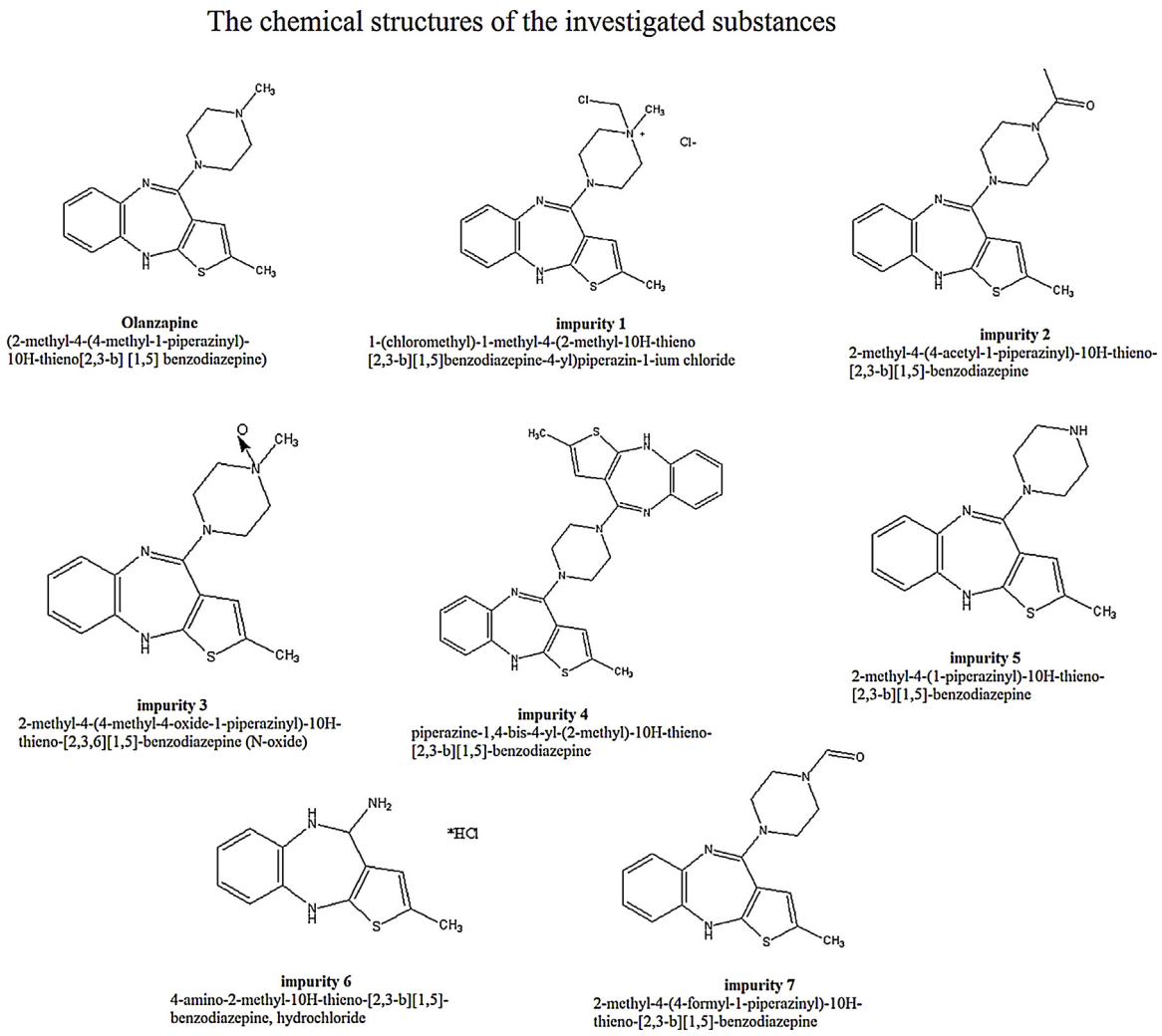

Fig. 1. The chemical structures of the investigated substances.

there are not many publications on the topic of AQbD approach in HILIC which makes it harder to apply on specific problems. AQbD methodology has been implemented in the development of two isocratic HILIC methods by our research group [11,12]. In those papers challenges have been successfully overcome regarding the HILIC specificities. Gradient elution on itself is more complicated then isocratic, and combined with the HILIC system it becomes a great challenge for the method development. Numerous gradient RP-HPLC techniques [13–16] have been developed in accordance with QbD methodology, but this is the first ever application for HILIC gradient method in the literature. Having in mind regulatory recommendations and lack of literature data about this topic, in this paper, AQbD approach was chosen for the method development of HILIC method with gradient elution for the mixture of olanzapine and its seven impurities. Olanzapine is an atypical antipsychotic drug commonly used for the treatment of schizophrenia [17]. Impurities investigated in this paper, for the reason of simplicity, are called impurity 1–7. Structures of all eight substances with their IUPAC names are presented in Fig. 1.

Official related substances from the European Pharmacopoeia 8.0 [18] and American Pharmacopoeia 38 [19] are related substance C (impurity 1) and related substance D (impurity 3). All the other impurities are not official in the above mentioned Pharmacopoeias. Impurity 4 is characterized as the oxidation product of olanzapine [20], while impurities 5 and 6 are its process impurities [21,22]. Apart from the above, two impurities (impurity 2 and 7) that are investigated in this paper are not official, nor examined in any other works.

Literature survey revealed several papers dealing with: HPLC determination of olanzapine in dosage forms (tablets) [23], LC–MS/MS (liquid chromatography – tandem mass spectrometry) determination of olanzapine alone or with different impurities in biological samples [24–26]. Furthermore, stability indicating methods for the monitoring of olanzapine and related substances also exist in the literature [27,28]. There were no HILIC methods for olanzapine found, all of the above are RP-HPLC methods. The advantages of HILIC over RP methods are well documented. First of them is its remarkable compatibility with mass spectrometry [2,3], which is usually the detection of choice, especially for the bioanalysis. Another advantage is the phenomenon that less polar analytes elute earlier due to the nature of stationary phase as well as the retention mechanisms which could be of great importance when tracking new impurities. Taking all this into account, the complexity of HILIC methods and problems that gradient elution mode brings with itself, it was assumed that the application of AQbD methodology would be challenging, while the obtained design space would be relatively small. Therefore, in this paper, the first ever HILIC gradient method was developed in accordance with AQbD, for the test mixture of olanzapine and its seven impurities.