Journal of Pharmaceutical and Biomedical Analysis 104 (2015) 17–20

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

Simple and rapid high performance liquid chromatography method for the determination of polidocanol as bulk product and in pharmaceutical polymer matrices using charged aerosol detection

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ARTICLE INFO

Article history:
Received 21 August 2014
Received in revised form 5 November 2014
Accepted 6 November 2014
Available online 20 November 2014

Keywords:
Assay
Dissolution
Charged aerosol detection
High performance liquid chromatography
Polidocanol
Pharmaceutical analysis

ABSTRACT

Currently, neither the European nor the United States Pharmacopoeia provide a method for the determination of polidocanol (PD) content despite the fact that PD, besides being an excipient, is also used as an active pharmaceutical ingredient. We therefore developed a method where the PD content was determined using a Kinetex C_{18} column operated at 40 °C with water–acetonitrile (15:85, v/v) as mobile phase. A Corona® charged aerosol detector was employed for the detection of PD that is lacking a suitable UV chromophore. The method was fully validated. Additionally, the method was applied for the determination of PD release from a pharmaceutical polymer matrix consisting of poly-ε-caprolactone and poly(lactic-*co*-glycolic acid) and PD.

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1. Introduction

Polidocanol (PD) is a heterogeneous compound consisting of ethers of mainly lauryl alcohol with polyethylene glycols of variable chain length with an average of nine ethylene oxide monomers (Fig. 1). It is widely used as an O/W emulsifier in pharmaceutical and cosmetic products [1]. PD also serves as an active pharmaceutical ingredient (API) as local anesthetic and antipruritic substance, and in sclerotherapy [2]. Furthermore, ethoxylated alcohols are extensively used in household cleaning products [3]. In addition, PD was recently employed to increase the protein release from polymer matrices [4].

Only a few procedures for the determination of PD in pharmaceutical formulations are reported. Quantitative thin layer chromatographic methods were described [5,6], but such methods are no longer considered to be state of the art. Numerous HPLC methods for the determination of ethoxylated alcohols using UV detection after derivatization [7], evaporative light scattering detection [8–13] or mass spectrometry [14–17] are reported, as their determination in waste water is of great importance in environmental analysis.

The European Pharmacopoeia (Ph. Eur.) addresses the dual use as excipient and as API in two separate monographs (macrogol lauryl ether as excipient [18] and lauromacrogol 400 as API [19]). In the API monograph, the specifications for impurities are tighter, e.g., the amounts of free lauryl alcohol and free polyethylene glycol as well as alcohols of differing chain length are restricted. No limits for these impurities are given in the excipient monograph as well as the USP monograph (polyoxyl lauryl ether, [20]).

Because the major pharmacopoeias do not provide an assay method, the aim of this study was to develop and validate a potential compendial method suitable for routine analysis of PD content. Here, a Corona® charged aerosol detector (CAD) was used. Like an ELSD, the CAD is an aerosol-based detector. The mobile phase is nebulized with nitrogen and the resulting droplets are dried in a heated tube. The remaining analyte particles are charged through adsorption of second stream of nitrogen that was charged by passing a corona needle. The electric charge is measured with an electrometer. The resulting signal is proportional to the analyte mass. The CAD is capable of detecting all non-volatile and some semi-volatile substances giving a response regardless of the chemical properties of the analyte [21] and is therefore well suited for PD detection, which lacks a UV chromophore.

Abbreviations: CAD, charged aerosol detector; PD, polidocanol.

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http://dx.doi.org/10.1016/j.jpba.2014.11.012
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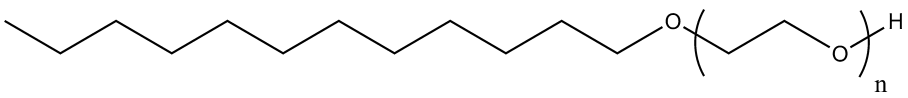

Fig. 1. Structural formula of polidocanol (PD). The number of ethylene oxide $n = 3–23$ for PD used as excipient and $n = 9$ for PD used as API.

2. Materials and methods

2.1. Reagents and material

Ultra-pure water (>18.2 MΩ) was delivered by a Milli-Q Synthesis water purification system (Millipore, Billerica; MA, USA). Gradient grade acetonitrile and lauryl alcohol were purchased from VWR International (HiPerSolv Chromanorm®) (Darmstadt, Germany), and polidocanol (Macrogoli aether laurilicum 9, Ph. Eur. 6.0) and polyethylene glycol 1500 from Fagron (Barsbüttel, Germany).

2.2. Instrumentation

Measurements were carried out on an Agilent 1100 LC system (Waldbronn, Germany) equipped with a binary pump, an online degasser and a thermostated column compartment. A Corona® CAD (Thermo Scientific, Idstein, Germany) was used for the detection. The gas inlet pressure (nitrogen) was 35 psi, the filter was set to "none" and the range to 100 pA.

2.3. Chromatographic conditions

The optimized method makes use of a Kinetex C_{18} (100 × 3.0 mm, 2.6 μm particle size) analytical column (Phenomenex, Aschaffenburg, Germany). The column compartment was maintained at 40.0 °C. The mobile phase consisted of water–acetonitrile (15:85, v/v) at a flow rate of 0.6 mL/min. The injection volume was 10 μL. The sample solution was prepared by dissolving PD in the mobile phase and diluting with mobile phase to a concentration of 50.0 μg/mL. The PD content was calculated using a reference solution prepared in the same way as the sample solution.

3. Results and discussion

3.1. Method development

The aim of the study was to develop a rapid HPLC method for the content determination of PD. The different PD homologues should be eluted as one single peak, which is separated from potential impurities present in the sample, i.e., lauryl alcohol, polyethylene glycol. Reversed phase chromatography is optimally suited as it suppresses the separation according to the number of ethoxylate units [22].

Initially, the retention behavior of PD at various contents of acetonitrile in the mobile phase (70/75/80/85/90%) was investigated (Fig. 2). Utilizing acetonitrile contents of 75% and below, the different PD species were partly separated and eluted over a broad span of time, thus aggravating its proper integration. A narrow PD peak was observed when using 90% acetonitrile as mobile phase. However, the PD peak was not sufficiently separated from the injection peak, indicated by a retention factor $k < 1$ ($k = 0.94$). A mobile phase composition of water–acetonitrile (15:85, v/v) was considered to be best suited. The different PD species appeared as one single peak with sufficient retention ($k = 1.20$, retention time 1.7 min).

The influence of the column temperature on the peak shape was studied. A reduction of 30% of the peak width at half height was achieved at 40 °C compared to 25 °C.

Thus, the separation was therefore carried out at 40 °C with a mobile phase consisting of water–acetonitrile (15:85, v/v).

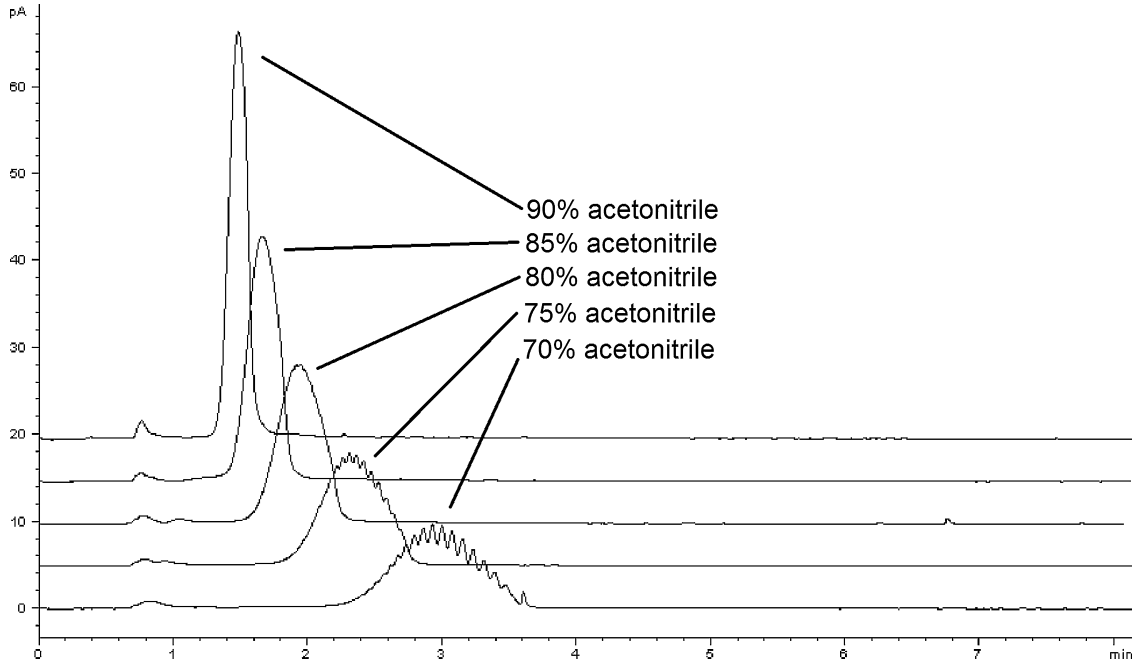

Fig. 2. Influence of the content of acetonitrile in the mobile phase on peak shape and retention time of the polidocanol peak (50 μg/mL). Mobile phase flow rate 0.6 mL/min; column temperature 40 °C; detection CAD.

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