Talanta 119 (2014) 312–319

Contents lists available at ScienceDirect

Talanta

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

Implementing the contamination prevention programs in the pesticide industry by infrared spectroscopy

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ARTICLE INFO

Article history:
Received 14 June 2013
Received in revised form
24 October 2013
Accepted 30 October 2013
Available online 6 November 2013

Keywords:
Infrared spectroscopy
Contamination prevention
Pesticide manufacturing

ABSTRACT

An infrared spectroscopy based methodology has been successfully developed to implement contamination prevention programs in the pesticide industry. Sensitivity of the IR procedure, traditionally considered the Achilles Hell of the technique, has been improved by using a transmission cell with an open upper side, an internal volume of 35 μL and an optical pathlength of 0.5 mm, providing detection limits of 32 mg L^{-1} for folpet and 48 mg L^{-1} for cymoxanil. The manufacturing of folpet and cymoxanil was employed as an example and the IR methodology was validated for the implementation of contamination prevention programs in the pesticide industry. The swab test and rinsate method were employed as sampling methods and results obtained by both were compared and correlated. Samples were analyzed from a qualitative and quantitative point of view. Qualitative information can be obtained by comparing the sample spectra with those of a new IR spectral library with approximately 50 entries of pesticide standards. Positive identification of folpet in all the analyzed samples was obtained. Other pesticides present in swab and rinsate samples positively identified by IR and confirmed by gas chromatography–mass spectrometry (GC–MS), were metalaxyl and chlorpyrifos methyl used in the manufacture of previous formulations. The amount of folpet in the swab and rinsate samples obtained by the developed IR method was compared with those of a reference procedure, being statistically comparable.

1. Introduction

The development of appropriate cleaning validation programs is receiving especial attention in different industrial sectors as a part of the quality control guidelines of the manufacturing process. It is particularly true in the pharmaceutical, biotechnological and cosmetic sectors, especially in plants with equipment dedicated to multi-product manufacture or packaging, where it is necessary to validate cleaning procedures because it is a regulatory requirement and it also assures, from an internal control and compliance point of view, the quality of the process [1–3].

Reactors cleaning validation is being gradually incorporated in the pesticide industry where the prevention of the contamination of commercially available pesticide products with residual impurities is an issue of growing concern for pesticide manufacturers, tollers and packagers [4]. It is well known that contamination of a commercial product with impurities of other pesticide can result in adverse effects on sensitive treated crops or non-target species and may trigger regulatory issues. Moreover, those incidents may also damage the reputation of the manufacturer company [3].

The assessment of the cleaning method capability implies the process of providing documented evidences that the cleaning methods employed within a facility consistently controls potential carryover of active products into the subsequent product to a concentration which is below predetermined levels. This process implies four key elements: (i) definition of the correct cleaning levels, (ii) establishment of appropriate manufacture equipment cleaning methods, (iii) development of appropriate analytical methodologies to optimize and validate the cleaning procedures and (iv) correct documentation of the aforementioned elements.

There is a lack of legislation regarding contamination prevention in the pesticide manufacture industry and only the USA Environmental Protection Agency (EPA) published in 1996 a notice addressed to manufacturers, formulators, producers and registrants of pesticide products regarding the maximum toxicologically significant levels of impurities of pesticide active ingredients present in technical grade active ingredients or products produced by an integrated system [5]. In this document, the EPA defined the toxically significant levels of contaminants as a function of the type of contaminant and the type of pesticide that is contaminated, establishing nine categories where the toxicological significant levels range from 1 to 1000 ppm.

Cross contamination in phytosanitary production plants could be an important problem from the environmental or legislative point of view. In a multipurpose non-dedicated production line, they can be

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http://dx.doi.org/10.1016/j.talanta.2013.10.062

manufactured pesticide products to be commercialized in specific areas such as the European Union (EU) or the USA together with products to be exported worldwide and that are not approved in EU and USA. So, the presence of residues of not approved active ingredients in pesticide products to be commercialized in a market due to cross contamination during the production step could be a serious problem [3].

Any analytical methodology used in the contamination prevention programs can be divided into two parts, sampling and detection. The most prevalent sampling method is based on the analysis of the last rinsate after having flushed a cleaning medium through the equipment [3]. However, the analysis of the rinsate does not guarantee that the impurities are below the defined level in the succeeding product, especially in the analysis of solid formulations, because previously manufactured products may remain in the equipment in the form of lumps located in dead spaces of the production line and may dislodge during the manufacturing of succeeding products [3]. On the other hand, typical analytical methods for residue analysis include gas chromatography–mass spectrometry (GC–MS) and liquid chromatography (LC) with diode array detection [6] to achieve the selectivity and sensitivity required. In those methods, the time for sample preparation and analysis typically means that results are available between hours or days from the collection of samples. Thus, it implies a considerable effort, in terms of time and money, to appropriately validate a cleaning procedure.

Because of that, in this paper, a fast infrared (IR) spectroscopy based methodology has been developed to implement contamination prevention programs in the pesticide industry. Due to its intrinsic characteristics, IR spectroscopy provides a fast and less expensive alternative to chromatographic procedures that reduces solvent consumption and minimizes waste generation [7]. However, sensitivity has been traditionally considered the Achilles Hell of the technique, and spectroscopists are continuously looking for methods to improve the limits of detection and make possible trace level analysis [8].

The use of transmission measurements with increased optical pathlength cells combined with reduced internal volumes can result in a good choice in order to provide an improved sensitivity of IR measurements, especially in those cases where the solvent used is a chlorinated one, such as chloroform. Thereby, in the present study it has been implemented a transmission cell with an open upper side to improve the sensitivity of the IR control method, providing detection limits of the order of parts per million, without sacrificing the simplicity which could be appropriate for the monitoring of the contamination prevention programs.

The production line selected to implement the contamination prevention program of a pesticide company has been one devoted to the manufacturing of solid products, because a successful cleaning procedure is usually harder to achieve than in the case of liquid formulations. Using the manufacturing of folpet and cymoxanil formulations as example, the methodology was validated and results were compared with those obtained by a LC reference procedure. It should be mentioned that sampling has been performed using the swab methodology and rinsates. The swab is recommended in the cleaning verification programs of the pharmaceutical industry [9] and it was done in different points of the inner surface of the mixers of the production line. Additionally, the rinsate of the manufacturing line was analyzed to find a correlation between both values.

2. Experimental section

2.1. Reagents

Folpet and cymoxanil Pestanal grade standards were obtained from Dr. Ehrenstorfer (Augsburg, Germany). Kaolin technical grade standard, used as inert material in the pesticide industry and for cleaning the production line, was kindly provided by a Spanish pesticide manufacturing company.

All the solvents used in this study were HPLC grade or higher. Acetonitrile was provided by VWR (Fontenay-sous-bois, France). Methanol was acquired from Panreac (Barcelona, Spain). Ethanol, 2-propanol and chloroform, stabilized with amylene (150 $\mu g\ mL^{-1}$), were purchased from Scharlau Chemie S.A (Barcelona, Spain). Water for the LC analysis, with a maximum resistivity of 18.2 M Ω, was obtained from a Milli-Q Millipore system (Bedford, MA, USA).

Stock solutions of folpet and cymoxanil were prepared in chloroform at a concentration level of 5000 $mg\ L^{-1}$. A calibration line ranging from 25 to 1000 $mg\ L^{-1}$ was prepared by appropriate dilutions of the stock solution in chloroform for IR analysis.

2.2. Infrared spectroscopy

IR spectra were recorded using a Tensor 27 FTIR spectrometer from Bruker (Karlsruhe, Germany) equipped with a DLaTGS detector. Spectra were obtained by coadding 10 scans at a resolution of 4 cm^{-1} and a scanner velocity of 10 kHz HeNe frequency, from 4000 to 800 cm^{-1}. For instrumental and measurement control, spectra treatment and data manipulation, it was employed the OPUS program (version 6.5) from Bruker.

In this study, a transmission cell with an open upper side (see Fig. 1a) has been used to improve the sensitivity of the method without sacrificing the simplicity. Thus, a standard transmission flow cell with 2 mm thick CaF_2 windows has been equipped with two Teflon spacers providing a pathlength of 0.5 mm and an internal volume of approximately 35 μL.

Once the cell was assembled, standard and sample absorbance were measured by transmission mode using manual introduction of solutions inside the cell, using a Hamilton 50 μL syringe (Bonaduz, Switzerland) and chloroform as background. Cleaning of the cell was achieved by three sequential injections of chloroform blank solutions.

2.3. Swab sampling procedure

For swab sampling procedure, TX®715 Large Alpha® Sampling Swab (CleanTips® Swabs) from ITW Texwipe (Kernersville, NC, USA) were used. They are double layer polyester swabs specifically engineered for cleaning validation purposes. The swab handled is notched to snap off the head for convenient sample handling and the heads of the polyesters swabs were thermally bonded to the handles without adhesives, avoiding possible contamination during analyte extraction. The swabs were also laundered by the manufacturer to minimize inherent non volatile residues or particulates that could affect the sensitivity and selectivity of the analysis [10].

To simulate the cleaning validation of manufacture equipment surfaces, polished stainless steel and iron, with different oxidation degrees, plates (5 cm × 5 cm) were used in laboratory recovery studies. 100 μL of folpet-cymoxanil (1:1) stock solutions, corresponding to 30, 35 and 40 $\mu g/25\ cm^2$ area, were directly spiked onto the plates, covering homogeneously the complete surface of the plate and they were allowed to dry in the fume hood. All samples were prepared in triplicate. For recovery experiments, the swabs were wet via their immersion into a 2 mL acetonitrile solution. Swabbing implies a systematic multi-pass of the soaked swab over the defined area. In our case, we used eight side by side strokes vertically, eight horizontally and eight each with the flip side of the swab in each diagonal direction. The soaked swab should be firmly passed and, after that, the swab stem was cut approximately 1 cm above the swab head and transferred to a vial containing 2 mL acetonitrile. The swab extraction procedure was repeated two times and the extraction solutions were mixed, evaporated to dryness, reconstituted in 100 μL chloroform and analyzed by IR.