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Analytical protocol for the sensitive determination of mannitol, sorbitol and glucose containing powders in pharmaceutical workplaces by ion chromatography using a pulsed amperometric detector

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ABSTRACT

Workers in the pharmaceutical industry can potentially be exposed to airborne dusts and powders that can contain potent active pharmaceutical ingredients (API). Occupational hygienists and health and safety professionals need to assess and ultimately minimise such inhalation and dermal exposure risks. Containment of dusts at source is the first line of defence but the performance of such technologies needs to be verified, for which purpose the good practice guide: *assessing the particulate containment performance of pharmaceutical equipment*, produced by the International Society for Pharmaceutical Engineering (ISPE), is a widely used reference document. This guide recommends the use of surrogate powders that can be used to challenge the performance of such containment systems. Materials such as lactose and mannitol are recommended as their physical properties (adhesion, compactability, dustiness, flow characteristics and particle sizes) mimic those of API-containing materials typically handled. Furthermore they are safe materials to use, are available in high purity and can be procured at a reasonable cost. The aim of this work was to develop and validate a sensitive ion-chromatography based analytical procedure for the determination of surrogate powders collected on filter samples so as to meet analytical requirements set out in this ISPE guide.

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1. Introduction

Workers in the pharmaceutical industry can be exposed to airborne dusts and powders that may contain potent active pharmaceutical ingredients (API). Occupational hygienists and health and safety professionals need to assess and ultimately minimise such inhalation and dermal exposure risks. Containment of dusts at source is the first line of defence but the performance of such technologies needs to be verified, for which purpose the ISPE good practice guide: *assessing the particulate containment performance of pharmaceutical equipment*, and now in its second edition is a widely used reference [1]. This document provides guidance and consistent methodologies for evaluating the particle containment (particulate emissions) of pharmaceutical equipment and systems.

In this guide the use of surrogate powders, e.g. mannitol, to challenge the performance of containment systems is recommended as their physical properties such as: adhesion, compactability, dustiness, flow characteristics and particle sizes often mimic those of API containing powders typically handled. They are safe materials to use, are available in high purity and can be procured at a reasonable cost. From an analytical viewpoint, being water soluble, they are relatively easy to handle in the laboratory.

This challenge function involves introducing a known quantity of a surrogate powder into a containment system and verifying its performance by ascertaining the extent of loss of material into the wider working environment, i.e. the fraction of surrogate powder that escapes from the containment system. By measuring the levels of surrogate material in air, through filter sampling and subsequent laboratory analysis, the extent of loss can be quantified and hence an estimation of the containment efficiency made. Similarly, assessment can be made on dusts sedimented on work surfaces through swabbing and subsequent analysis. A useful overview of containment testing for pharmaceutical equipment performance has been described by Petroka [2].

The aim of this paper is to describe our approach to the development and validation of a sensitive analytical procedure for

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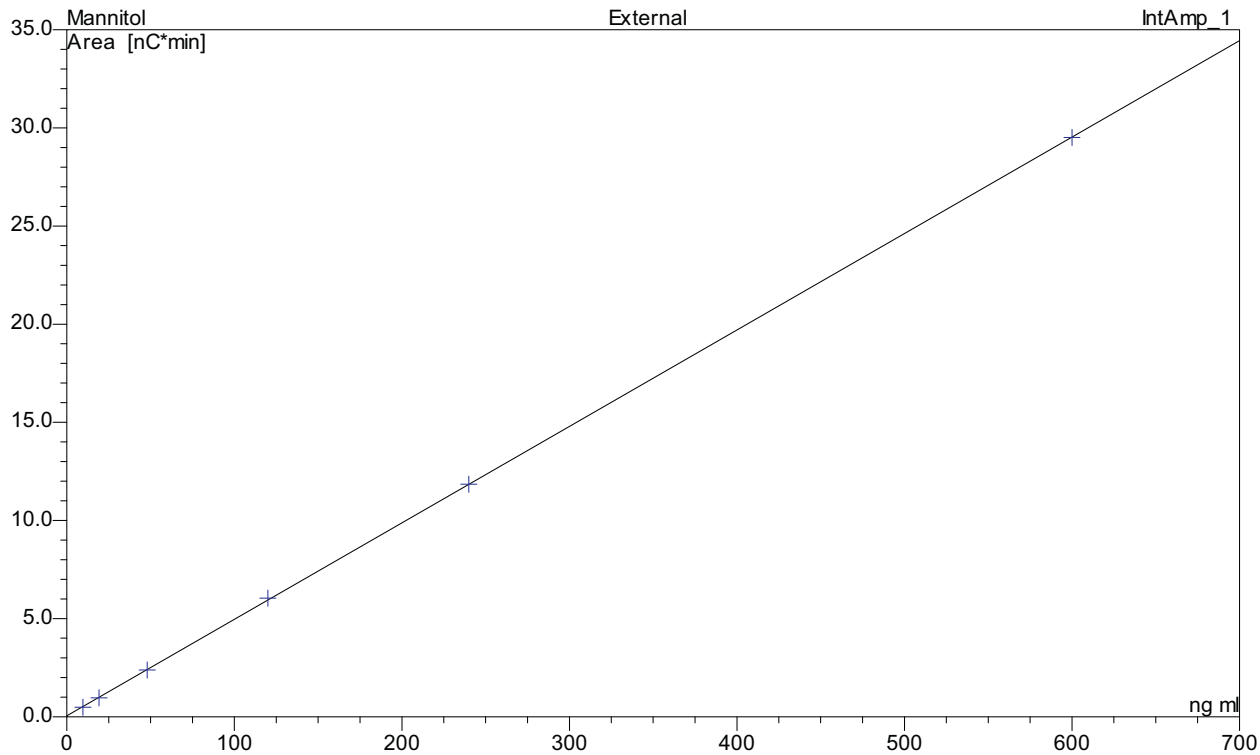

Fig. 1. Calibration plot for Mannitol over 0–600 ng mL^{-1} range.

the determination of mannitol, sorbitol and glucose surrogates collected on air filter samples. The approach described is also amenable to swab samples although this not reported here. This methodology involves leaching sampling media in water, filtration of the resultant solution and analysis using an ion chromatography (IC) system equipped with a pulsed amperometric detector (PAD). This work builds upon earlier HSL work in which an IC-PAD method for the determination of lactose [3] was developed in support of recommendations in the first edition of the ISPE guide [1].

2. Materials and methods

2.1. Instrumental considerations

Initially it was assumed that the method developed for lactose could be extended to encompass a number of additional surrogate materials recommended now for inclusion in this revised ISPE guide [1]. This original method used a Dionex PA20 5 μm column (3 mm × 150 mm with a 3 mm × 50 mm guard) and a 150 mM NaOH eluent [3]. Modifying this method, by varying the eluent concentration, did not produce the desired result of resolving the selected glucose, fructose, lactose, mannitol, sorbitol and sucrose surrogates from each other. An alternative approach using a Dionex MA1 4 mm × 250 mm column and 480 mM NaOH eluent was then examined [4]. Here, mannitol and sorbitol separated with good resolution but glucose and fructose peaks were found to co-elute. Furthermore the retention times for lactose and sucrose were too long, with a total sample run-time of ca. 45 min.

As gradient elution capability was not available at the Health and Safety Laboratory, it was decided that the existing method for lactose would be retained (sample run time of ~8 min) and the new method validated now only for mannitol, sorbitol and glucose (sample run time of ~25 min). It is anticipated that future measurement of surrogates would focus on the use of such substances. In summary the instrumental conditions presented in Table 1 were those subsequently used for method validation purposes.

2.2. Preparation of calibration standards

Stock standard solutions, at a nominal 1000 mg L^{-1}, were prepared by dissolving known masses of high purity surrogate materials, procured from a number of different vendors, in deionised water. From these single compound standards, a composite stock calibration standard solution was prepared at a nominal 24 mg L^{-1} from which working calibration standards and a limit of detection (LOD) test standard were prepared (Table 2).

Calibration verification standards were prepared in the same manner but using starting materials from a different vendor or from a different lot number to those used for calibration purposes.

2.3. Validation strategy

The ISPE guide [1] does not provide detail on how to validate an analytical method for the determination of surrogate analytes. For

Table 1
IC-PAD instrument conditions.

Instrument	Dionex DX-500
Autosampler	Dionex AS50
Pump	Dionex IP25
Column oven	Dionex AS50
Detector	Dionex EC50
Analytical column	Dionex MA1 4 mm × 250 mm
Guard column	Dionex MA1 4 mm × 50 mm
Column temperature	40 °C
Eluent	480 mM NaOH, carbonate free
Flowrate	0.5 mL min^{-1}
Detection technique	Pulsed amperometry
Waveform	Waveform A (Dionex, TN 21)
Injection volume	200 μL

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