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REVIEW ARTICLE

The Containment Performance Verification and Determination of Surrogate Particles

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ABSTRACT

Several advances in medicines and medicinal values help in curing diseases and in improvement of health care systems. The biopharmaceutical industry is committed in ensuring that the medicine is useful to all patients. Success of the biopharmaceutical industry is highly depended on the invention and growth of medicines that can improve human health. Nowadays pharmaceutical industry is facing several key challenges. The workers in biopharmaceutical industry are exposed to surrogate powders and airborne dusts which contain harmful Active Pharmaceutical Ingredients (API). This paper proposed the surrogate powder application in testing the containment system performance. Materials such as lactose and mannitol are suggested as their physical characteristics such as compatibility, dustiness, adhesion, particle sizes and flow properties are reflecting those of active pharmaceutical ingredients. Moreover they are safe, highly pure and can be obtained at a reasonable cost. This paper is aimed at developing and validating an ion-chromatography based analytical technique for determining surrogate powders such as mannitol, sorbitol and glucose. Finally, a standardised approach is used for evaluating the containment performance of a planned system of dust collection that would help in making a new manufacturing area.

Keywords: Containment system, LOD, Mannitol, Biopharmaceutical industry, Calibration standards.

1. INTRODUCTION

During the past decade, state governments have worked hard to attract and retain biopharmaceutical companies and associated life science industries as they identified that these industries are needed for a strong economic development. The appropriate selection and operation of contained dust collection device pose a great threat to workers in pharmaceutical plants for a variety of reasons varying from environmental necessities and employee's health and safety to production efficiency and cleanliness. Surrogate testing is the most important and valuable tool which is used to confirm that the contained dust collectors are meeting the necessities for controlling the hazards, which is related with the materials being treated and any appropriate better manufacturing practice.

[1] established a method to assess the powder dustiness by the consumption of a small amount of samples. Here, an optimized measurement condition for a commercially available dust meter was established. By using the optimized test conditions, the dust meter mode, the flow rate, the drum rotation speed, the total measurement time and sample loaded weight were determined. The setup conditions of the dust meter are very much valuable to pharmaceutical industries, particularly, at the early stage development and principally for expensive materials, because the consumption of a small amount of samples can evaluate the quantity of air-borne dust with accuracy. From an analytical viewpoint, water being soluble, they are comparatively easy to handle in the manufacturing laboratory [2].

To overcome this challenge, functions introduce a well-known amount of surrogate powder into the containment system and confirm its performance by determining the degree of material loss into the wider working environment, i.e. the quantity of surrogate powder that escapes from the containment

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system [3]. By measuring the surrogate material levels in air, through filter sampling and following laboratory analysis, the extent of material loss can be quantified and therefore an estimation of the containment efficiency can be made. The containment testing for pharmaceutical equipment performance was described in [4]. Depending on their effectiveness, APIs can be placed into control bands. This is the first step in a systematic method to ensure safety of workers, when they are handling strong and highly strong APIs. Each control band should be related with a safe handling guideline. [5] described in detail about the material strength that should be used for handling the diverse environments encountered in the workplace. Generally, most parties define a strong API as one with an Occupational Exposure Limit (OEL) below10 $\mu g/m^3$ and highly strong API as having an OEL below 1µg/m3. [6] highlighted that guidance should be provided to the workers in pharmaceutical plants before handling the strong compounds. It is helpful to understand the possibility of potential hazards caused by the compounds. Hence suitable control measures are selected. Thus the selection of workplace controls should be made the target exposure points to these hazards, thus reducing the risk of becoming accidentally exposed to the compound. [7] explains about a method for estimating the airborne powder concentrations at the work place using powder dispersibility and another method for designing a powder containment facility using airborne powder concentration [8]. [9] investigated the potential advantages and difficulties of mixing predictive model equations in models of unit manufacturing methods. The method described uses metamodels and semantic web technology to relate equations as objects in downstream activities. [10] described a method for surrogate-based optimization using kriging response surface modelling combined with the analysis of black-box feasibility in order to resolve constrained problems of noisy optimization in less computational time. [11] presented a methodology which is used to enhance a direct compaction of tablet manufacturing process for the minimization of final product characteristics variability while the constraints guarantee that procedure operation and product quality are within the predefined set of ranges. [12] emphasized growths in the flow sheet modelling for pharmaceutical processes and also discussed about the optimization of these complex process models. [13] explained about the challenges associated with modelling particulate methods and also discussed the modelling approach involving a continuous process of both feeding and blending. [14] demonstrated that such a data potential is used for modelling first-order contact to assess the potential worker contact and transmission of active surrogate powder ingredients into ventilation systems and recommended that excessive dust concentrations could be reached with the highest dustiness levels. [15] discussed about the methodologies of optimization, which is used for the improvement of batch and continuous manufacturing in pharmaceutical industry. Challenges in the application of optimization methods in pharmaceutical manufacturing have been overcome in this proposed method along with a future outlook of the field and its place in pharmaceutical process and product design.

2. METHODS AND MATERIALS

2.1. Performance of containment system

This proposed method requires information from the existing methods in order to mention the design of both the Containment Performance Target (CPT) and containment system. The main goal of this method is to verify the containment performance and prove that this airborne concentration will not generally be exceeded. The containment performance is generally defined as the concentration of airborne particulate measured around the containment device and during simulated operations for the operator's breathing zone. The International Society for Pharmaceutical Engineering (ISPE) guide contains the detailed methodology for this evaluation. It also mentions an approach using a surrogate material in order to confirm the performance of the containment. The most commonly used surrogate materials are lactose, mannitol, sorbitol and glucose. Apart from that, other materials such as paracetamol and naproxen sodium may also be used. Therefore, these materials are chosen based on their comparatively low poisonous nature and those analytical methods which are available and is capable of identifying very low levels of these materials on filters, thus allowing airborne

samples have quantification at concentrations below the target of containment performance.

2.2. Data of the manufacturers' containment performance

The containment system performance of any single equipment piece is dependent on the circumstance use. Some of the factors which affect the containment system performance are

- The API quantity being handled.
- The particle size and powdered API properties.
- The integrity of the containment device.
- The nature of the operation.
- Operator practice and technique.

These changes correspond to the fixed containment performance that cannot be assigned to containment apparatus and is the important reason for the large number of definitive containment data accessibility in the public domain. Therefore the manufacturers of the pharmaceutical industry will tend to provide a wide range of containment performance values for their equipment. By using data from the public domain, the potential difference between the manufacturers demanded containment and the real performance can be demonstrated.

2.3. Instrumental considerations

As the gradient elution capability was not obtainable, lactose would be kept with the assigned method and a novel method is verified only for surrogate materials such as mannitol, sorbitol and glucose. It is expected that surrogate materials and future measurement would be more application oriented. Table A1 shows the instrumental conditions of IC-PAD and this process is further used for purposes such as system validation.

2.4. Calibration standards preparation

The standard solutions (1000 mg L^{-1}) were prepared by mixing high purity mannitol, glucose and sorbitol in a medium of deionised water. From these, a compound solution of stock calibration standard was prepared at a nominal 25 mg L^{-1}. A boundary of Loss On Drying (LOD) test is presented in table A2. The calibration plot for mannitol is shown in figure B1.

3. RESULTS AND DISCUSSION

The proposed method establishes the successful measures of sorbitol, mannitol and glucose. These surrogate particles are taken on air sampling filters made up of glass fibres. The validation method determined the complete LOD for 6, 6 and 12ng. Spike recoveries over different concentrations were normally between 80–100% and extracted LOD test solutions were obtained. The obtained validation results are indicated in tables A3–A6.

3.1. Verification of containment performance

Surrogate testing helps in providing factual information related to containment performance before setting up. This paves a way for the pharmaceutical industry to decide if the instrument under study meets the basic standards and guidelines for a specific project. This contains surrogate material applications for simulating an Active Pharmaceutical Ingredient (API) and to verify the efficiency of dust containment options for managing hazardous resources. The design of test conditions was carried out in such a way so that the mimic work place operations are as close as possible. Hence the health concerns of handling the actual active pharmaceutical ingredients are never incurred. A specialized independent laboratory works for carrying out the surrogate testing in order to validate the planned dust collection performance of a system that would help the industrial arena.

3.2. Simulated and sampling operations

A device which is used for the containment performance may not be assured by pharmaceutical industry, particularly if the essential performance descriptions are better than the pharmaceutical industry cited. Overall containment performances of devices are assessed from the factors and are highly unpredictable. Hence, prior to API handling in containment devices the performance of containment systems should be confirmed. Containment performance verification measures the performance of the contained system as constructed in the factory, when being upgraded in a Site Acceptance Testing (SAT) production facility. Various ancillary devices such as transmission equipment are fitted to an isolator. Also containment performance evaluation must be carried out

with the help of all devices. These evaluations are made available by standardised methods. These confirm that the target of the containment performance is accomplished. During Site Acceptance Testing (SAT) and Factory Acceptance Testing (FAT), the process of surrogate particulate containment performance verification must be carried out. Containment performance testing and verification should be carried out only by skilled occupational and industrial hygienists. Thus the use of these contained systems in the pharmaceutical industry offers the strong manufacture of highly strong API and can provide a better and safe working environment condition. Worker safety is another one factor which needs to be focussed on. It must be estimated by measuring the airborne worker exposure and should be correlated with the expected worker exposure during routine production operations. They are exposed to a strong API against a resultant occupational exposure limit (OEL).The last stage of the containment system performance evaluation uses a sensitive occupational hygiene analytical method. On-going evaluations give assurance that strong or highly strong APIs are being handled securely. Such methodology is frequently implemented in the biopharmaceutical industry, which states that new synthesised proprietary nature compounds do not have OEL's.

4. CONCLUSION

It is concluded that the surrogate monitoring estimates the containment of equipment effectiveness using materials which is less poisonous. In this paper, determination of instrumental LOD, LOH technique and sample stability of surrogate materials such as sorbitol, mannitol and glucose were performed. The sampling approach contains both surface samples and air samples. Glass fibre air sampling filters successfully capture the sorbitol, mannitol and glucose components and are measured by the IC-PAD technique. The Limit of Quantification (LOQ) determines and assesses the containment performance. Thus the results can be helpful in choosing containment equipment that are suitable for particular applications. Hence, employees in the pharmaceutical industry should also be assessed for API once the containment of a planned system of dust collection becomes functional in the laboratory.

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APPENDIX A

Table A1.Equipment conditions

Equipment	Dionex DX-500
Column oven	Dionex AS50
Pump	Dionex IP25
Auto sampler	Dionex AS50
Column temperature	40 ^{0}C
Analytical column	Dionex MA1 4 mm ×250 mm
Detector	Dionex EC50
Waveform	Waveform A (Dionex, TN 21)
Flowrate	0.5 mL min−1
Eluent	490 mMNaOH

Table A2.Representation of working calibration standards preparation

Solution used for calibration process	Diluted solution	Volume to be diluted to 60 ml	Resulting concentration
G	Standard solution for mixed calibration 25 mg L^{-1}	1.25	800
H	Standard solution for mixed calibration 25 mg L^{-1}	0.6	260
I	Standard solution for mixed calibration 25 mg L^{-1}	0.25	130
J	Solution for calibration C	30	58
K	Solution for calibration I	9	21.3
L	Solution for calibration I	5	10.5
Test in LOD	Solution for calibration G	0.6	7

Table A3 Result for the determination of an instrumental LOD

Surrogate particles	Test sample in LOD (6 ng ML^{-1})		Calculated value of LOD(ng ML^{-1})
	Mean recovery (%)	Standard deviation (%)	
Sorbitol	89	3.4	0.8
Mannitol	78	4.5	0.9
Glucose	78	5.5	0.9

Table A4.Result for the recovery tests in spiked filter

Surrogate particles	Low concentration (80 ng)		High concentration (1600 ng)	
	Mean recovery (%)	Standard deviation (%)	Mean recovery (%)	Standard deviation (%)
Sorbitol	90	1.5	97	0.8
Mannitol	93	2.0	98	0.4
Glucose	95	2.5	96	0.2

Table A5**.**Result for the determination of LOD technique

Surrogate particles	Low concentration (80 ng)		Calculated LOD method at a nominal 4ml	Calculated method limit of quantification (3.4x LOH method)
	Mean recovery (%)	Standard deviation (%)		
Sorbitol	96	3.6	8	24
Mannitol	98	3.4	8	24
Glucose	94	7.2	16	48

Table A6.Result for the determination of a sample stability

Surrogate particles	Low concentration (80 ng)		High concentration (1600 ng)	
	Mean recovery (%) (after 7 days)	Standard deviation (%)	Mean recovery (%) (after 7 days)	Standard deviation (%)
Sorbitol	95	1.6	101	0.2
Mannitol	104	2.5	98	0.4
Glucose	93	2.6	95	0.6

APPENDIX B

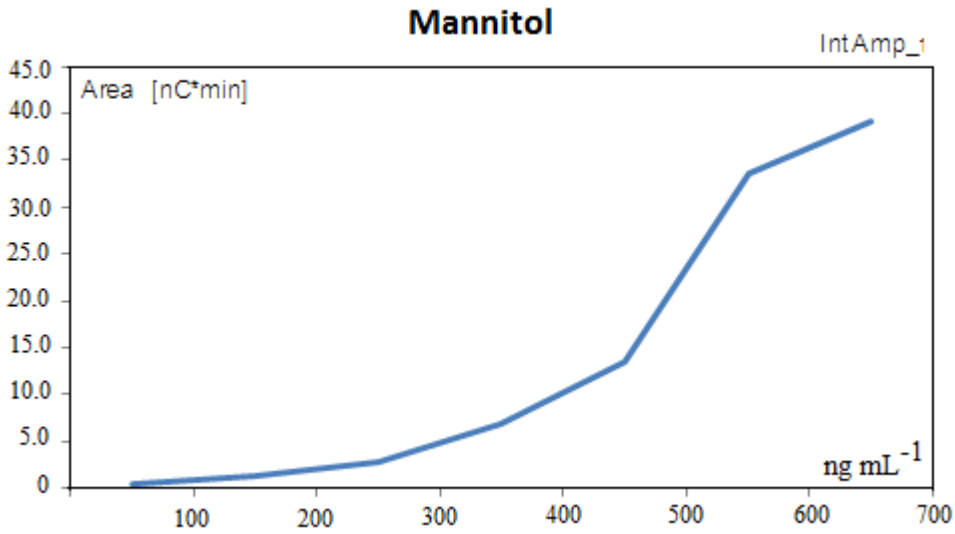

Figure B1.Calibration plot for mannitol over the range of 0–700 ng mL^{-1}