Nebuliser Issues To Be Improved For The Pulmonary Administration Of Nano Encapsulations

A. A. Desta [1], K. C. Carter[2], T. Gourlay[1]&A. B. Mullen[2]

[1]Biomedical Engineering, 106 Rottenrow East, Glasgow, G4 0NW, United Kingdom

[2]Strathclyde Institute of Pharmacy and Biomedical Sciences, 161 Cathedral Street, Glasgow, G4 0RE, United Kingdom

Summary

Nano based formulations which encapsulate drugs, nano-encapsulations (NE), can be used to provide economical and effective delivery of existing and novel drugs. When administered via the pulmonary route they can enhance therapeutic outcomes whilst reducing adverse side effects. They can be used for local or systemic delivery, broadening the types of conditions that can be treated by inhalation.

It is believed that atomising NEs developed as a simple colloidal suspension fluid rather than a dry powder format may offer clinical advantages. However, existing devices have a number of limitations with respect to delivery of these systems. This paper will highlight the aspects of current nebuliser devices that negatively impact NE viability and delivery efficiency. These drawbacks are being addressed in our ongoing work to develop a novel nebuliser. In addition, new data is presented surveying nebulisers in current clinical use based on anonymised adverse incident reports obtained from the UK's Medicines & Healthcare product Regulatory Agency (MHRA).

Plotting the findings in a priority matrix revealed that Increased NE reservoir concentration and device reliability are the most important variables, whereas issues such as ease of use and user error were the least important issues to the delivery and viability of NE.

It is concluded that NE integration for pulmonary administration needs device improvements to uphold the economic characteristics of NE.

Introduction

Liposomes and niosomes are NE that entrap medicine in a vesicle systems. They have proved a suitable delivery vehicle for drugs by enhancing cellular drug uptake and reducing the required drug dose for effective treatment. NE preparation methods mostly result in a colloidal fluid system. For pulmonary administration however, nebulisers have been shown to have a detrimental effect on NE causing aggregation, bursting and leakage of the encapsulations when atomising[1]. Various studies report that post-nebulisation NE drug leakage is approximately 40% resulting in significant delivery of un-encapsulated drug and wastage of lipids or surfactants [2].

As a result, transforming NE into a dry powder through freeze drying has become a post-production necessity. This addresses some of the instability issues when formulated as a suspension such as leakage, aggregation and sedimentation. Also, as a dry powder, NE can simply be inhaled through dry powder inhalers (DPI) instead of nebulisers which only deliver liquid based drugs [3].However, to prepare NE for freeze drying, further excipients such as lyoprotectants are also required to ensure steric stabilisation. These however increase production costs and result in additional toxicity concerns for pulmonary delivery [4]. The potential of NE inhalation therapy with nebulisers without resorting to freeze dried preparations is explored. Key existing nebuliser issues are also prioritized when developing a nebuliser for better NE administration.

Methodology

To effectively qualify the current needs for improvement, reported issues with nebulisers in research and clinics are explored. In order to highlight the key nebulisation issues associated with detrimental effect to NE, previous research articles are reviewed involving nebulisers and NE drug delivery; reporting non-formulation factors only. Thus avoiding issues in regards to NE suspension stability which has little to do with nebuliser device design.

MHRA incident report data is used to understand how the wider nebuliser therapy issues in clinics affect NE delivery. The anonymised nebuliser device incident report data was collected from 2011 to 2014 and categorized 72 incidents based on type of incident and subdivided by potential injury level.

Key nebuliser issues are displayed on a priority matrix of NE viability against the importance of delivering NE.NE viability refers to the intactness of the NE particles and NE delivery efficiency refers to their transport efficiency from the reservoir through the atomiser in to aerosol micro droplets and in the lung. The position of the issues in the priority matrix was based on the author's opinion formed through understanding the severity and impact on worst case scenarios.

Results

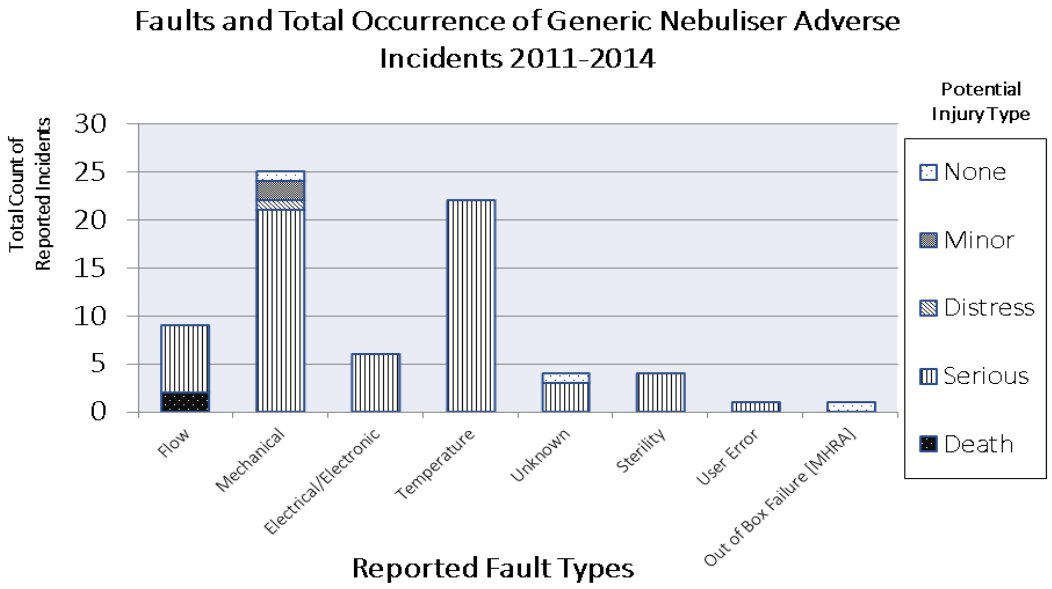

Figure 1: MHRA's nebuliser incident report between 2011 and 2014.

MHRA adverse incident reports with manufacturer, device model and location anonymised. Comparing reported device faults and total incident count, n = 72.

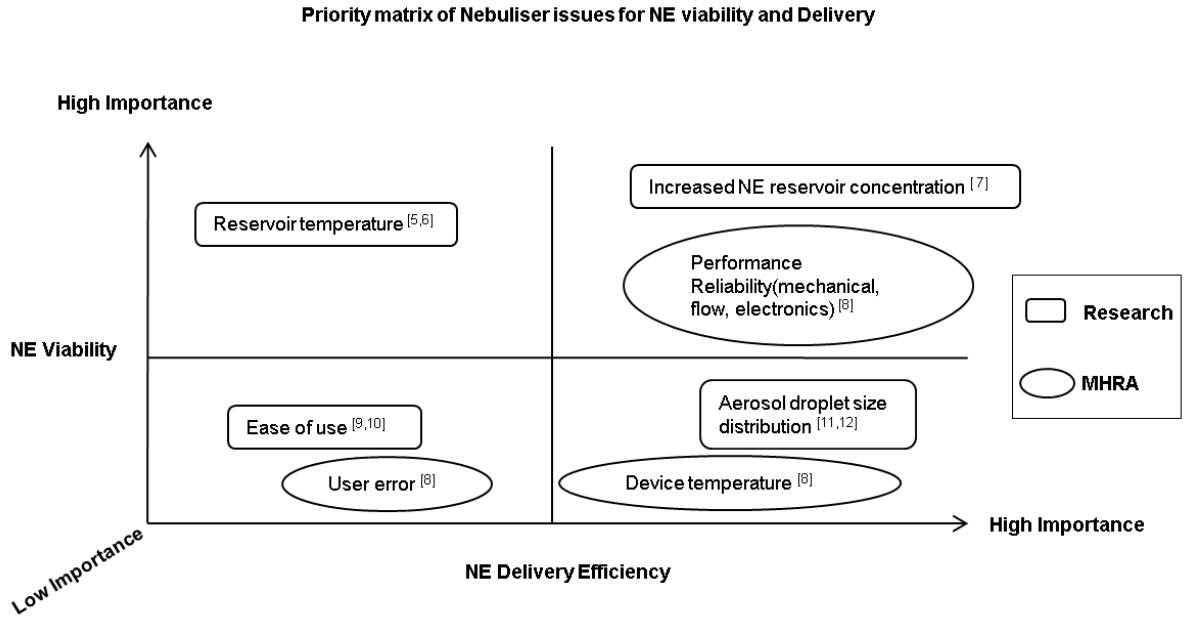

Figure 2: Priority index of nebuliser issues and their importance for the efficient NE viability and delivery.NE viability refers to the intactness and post nebulisation entrapment efficiency whereas NE delivery efficiency refers to the concentration of NE within the aerosol droplets and delivery of the aerosols into the lung. Upper right quadrant contains the highest priority and lower left quadrant is the lowest priority issues for both NE viability and NE delivery.

Discussion

Incident report findings are displayed as a bar chart in Fig. 1. Although 72 incidents in 4 years don't provide statistical significance, it does present the issues deemed adverse enough to be reported to the MHRA.

It is found that majority of the reported incidents had serious potential injury. Temperature and mechanical faults were found to be the highest number of reported issues. Flow related faults have been reported with two potential injuries of death and one reported actual injury of death. Flow faults are particular to air jet nebulisers where the driving gas can be either oxygen or air depending on the patient's clinical condition. Previous incidents have resulted from mistaking air and oxygen supply resulting in hypoxemia or hyperoxia[13, 14].

The gathered issues from both research and the MHRA incident reports were then displayed on a priority matrix in Fig.2. The importance levels are assigned based on their understood effect towards NE rather than statistical occurrence as it helps present the key priorities novel solutions should consider

The priority matrix shows that increased NE reservoir concentration is the highest priority issue for both the NE viability and delivery efficiency. This was previously noted in studies comparing aerosol output vs drug output where the emitted aerosol droplets had less NE concentration than the original solution. This results in higher NE concentration within the reservoir, leading to aggregation that causes leakage of encapsulated drugs and affects the size polydispersity of the NE [7].

Reservoir temperature is another issue that is significantly detrimental to the NE viability but less so with the NE delivery efficiency. Its detrimental effect of weakening the NE walls results in susceptibility to mechanical agitation from the atomisation process [5, 6]. MHRA incident reports associate temperature with serious potential injury and one actual serious injury. Although it is important to highlight that the incident report data associates 55% of reported temperature issues with "nebuliser compressor", which is only present in air jet nebuliser types [8]. These nebuliser types use a motor driven air compressor to provide the air jet and are normally fitted with a thermal switch which renders the device inoperable until it cools down. This affects NE delivery efficiency more than NE viability.

Mechanical issues are believed to arise from air jet nebuliser types. This is the only nebuliser that makes use of mechanical actuation to provide air jets for atomisation. The mechanical issues arise from the diaphragm air compressor which constitutes a motor, piston and valves. It is also believed that flow issue arises mostly from air jet nebulisers. The fault again is associated with the air compressor unit where the air flow circuit can be restricted or the air compression system composed of motor, piston or valve is not providing the necessary force to provide the advised flow rate emitted by the air compressor. Electronics faults are related by the internal circuitry in relation to arcing and potential of causing fire. These issues found in the MHRA incident reports were grouped into performance reliability. It is believed that issues such as mechanical, flow and electronics faults did not occur as a fundamental design flaw but rather as in use wear and tear of the device. Performance deviations can affect both the viability and delivery efficiency of NE.

One key performance index of nebulisers and an NE delivery factor is the aerosol droplet size. Control of aerosol droplet size determines the deposition profile of the drug ranging from the nebuliser passages through to the alveoli and exhaled drug [11].

Majority of the mentioned factors are underpinned by reliability of the device where functionality of the device is required over the course of the therapy and deviation of performance over time can affect both NE viability and delivery efficiency[9, 10].

In addition to reliability ease of use would be an essential feature in relation to treatment adherence. This would affect drug loading process, adherence to the therapy schedule and correct device operation. Therefore, incorrect operation will negatively impact both NE viability and delivery efficiency. Although ease of use can be countered with effective training there are signs in the industry where nebuliser design is incorporating autonomous features like breath sensors which only activate the atomiser during the first 80% of inhalation breath cycle to reduce loss of aerosol during exhalation [10].

Conclusion

This study helps to highlight key device issues which if improved will positively impact the viability and delivery efficiency of NE through nebulisers. Increased NE reservoir concentration and performance reliability are key issues in both NE viability and delivery efficiency. Reservoir temperature plays an important role in NE viability and aerosol droplet size as an important determinant of drug deposition.

Not associating the issues with nebuliser types helps bring focus to possible issues to minimize in the design of future nebulisers. The only exception was the temperature issue associated with Air jet nebuliser type. As it was important to distinguish the device temperature issue presented in the MHRA report from the reservoir temperature issue presented in research.

Although this paper focuses on NE inhalation therapy, improvement in reported issues is not limited to NE and can bring benefits to sensitive medication such as inhaled protein therapy.

The purpose of this study was to help guide decisions on which nebuliser issues to focus on when adapting future nebulisers for NE delivery. It is believed efforts for NE therapy integration should not be reserved to formulation activity only. But should incorporate device improvements to effectively adapt NE for inhalation therapy. Since NE are delivery vehicles, any effort in upholding their benefits will result as an economic advantage for drug delivery to the lungs.

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