Pharmatec's innovative filling process for pressurised metered dose inhalers

Pharmatec Solutions Ltd. specialises in innovative and sustainable manufacturing processes for pressurised metered dose inhalers (pMDIs), helping pharmaceutical companies provide continued access to lifesaving and environmentally friendly pMDIs for patients. In collaboration with Harro Höfliger, a global leader in powder handling and packaging systems, Pharmatec Solutions is advancing a streamlined pMDI filling process. This method involves precisely weighing the drug and excipients directly into the canister, thereby separating it from the propellant filling stage.

We invited Tony Clark, Managing Director of Pharmatec Solutions, to share insights on this innovative pMDI manufacturing method and its potential to revolutionise the transition to lower global warming potential (GWP) pressurised metered inhalers.

1. Can you tell us more on this approach for canister filling and what it entails?

Manufacturing pressurised canisters for aerosol delivery presents numerous challenges, particularly during the filling process of the formulation, which includes the drug, excipients, and propellant, into the primary container. Dry powder dosing into primary packaging containers, such as canisters or capsules, is a well-established process in the pharmaceutical industry, especially for manufacturing orally inhaled and nasal drug products (OINDPs). While several dry powder filling technologies are available, handling micronised dry powders with very fine, cohesive particles remains challenging. The drum filling technology offers a simple and effective solution for delivering accurate and repeatable doses, making it the most commonly used method for powders in OINDP manufacturing.

Hence, we came up with the idea of developing a simpler and cleaner way to manufacture pressurised products employing an established and proven powder filling technology by directly dosing the fine micronised active ingredient into the aluminium canister, crimp the valve and subsequently fill the pMDI with the propellant.

This initiative was also driven by the transition to more environmentally friendly propellants and the need to handle flammable, eco-friendly alternatives, such as hydrofluoroalkane 152a, to those currently used in the market. Since the adoption of the Kyoto Protocol in 1997 and the Europe F-Gas regulation in 2015, further amendments aim to reduce F-gas usage by over 80% by 2047 due to their contribution to global warming. These changes are expected to significantly impact the pharmaceutical industry, particularly inhalation products, which account for 2.4% of total F-gas emissions. Affordable alternative propellants with lower global warming potential (GWP), such as hydrofluoroalkane (HFA) 152a and hydrofluoroolefin (HFO) 1234ze, have been identified. Ongoing research

Lab drum filler

focuses on the re-formulation and development of low GWP pMDIs for asthma and chronic obstructive pulmonary disease (COPD).

Some of these re-formulated pMDIs are already well-advanced and undergoing clinical trials. For instance, Chiesi recently initiated a long-term Phase III clinical safety trial for a new carbon-minimal fixed combination of an inhaled corticosteroid and a long-acting bronchodilator. Similarly, GSK announced the start of Phase III trials for their HFA 152a version of Ventolin in 2024. Differences in the physicochemical properties of high and low GWP propellants, such as vapour pressure and density, lead to variations in aerosol behaviour, including evaporation rate and surface charge. These differences must be considered when re-formulating current pMDIs with more sustainable propellants like HFA 152a. Additionally, the higher flammability of this propellant necessitates the installation of entirely new filling lines in designated ATEX areas, often requiring pharmaceutical companies to build new facilities to accommodate production.

However, a two-stage direct powder filling approach can mitigate these challenges. This method allows the use of existing facilities with less stringent ATEX requirements, even for more flammable propellants. It eliminates the need for formulation skids with large volume mixing vessels containing propellants, enabling bulk storage of these propellants outside the facility. This significantly reduces the risks associated with handling new propellants, particularly HFA 152a, as there is no longer a need to mix propellant and powder inside the facility

2. So, in a nutshell what advantages will this process bring for manufacturing companies?

The two-stage direct powder filling approach can be employed in manufacturing pressurised canisters for the pharmaceutical, beauty, and personal care industries, addressing production challenges companies face and enhancing current manufacturing practices. This innovative method utilises existing, proven technologies. The primary benefits of this staged filling approach include increased efficiency in product manufacturing and independence from the capacity of pressurised mixing vessels. This adaptability makes it suitable for continuous batch production, which is highly attractive for various industries. Additionally, it eliminates changeover times and downtime for cleaning, as well as the need for recirculation when preparing new suspensions or solutions.

Moreover, by removing the requirement for a pressurised mixing vessel and decoupling propellant filling from active and inactive ingredient dosing, the approach mitigates some safety concerns associated with propellant flammability. This separation allows for easier retrofitting of existing facilities to accommodate HFA 152a pMDI manufacturing, saving pharmaceutical companies both time and money.

3. What would be the pathway from small scale production up to commercial?

This decoupled filling approach is already used in early development formulation screening studies, where the drug and excipients are directly weighed into open aluminium canisters using a laboratory balance and spatula, followed by valve crimping and propellant addition. We have integrated an automated powder dosing process into this existing method. Numerous formulations have been filled and stability studies conducted, showing results comparable to current practices.

Vacuum crimping, a standard pMDI manufacturing process step that ensures canisters are air-free, was assessed and found to have no impact on the powder filling method. This confirms the compatibility of the direct powder filling approach with standard valve vacuum crimping methods, simplifying the scale-up process.

Solutions for early development manufacturing are already available, as is readily available powder filling equipment suitable for pilot-scale production and early-phase clinical trials. These solutions can be seamlessly integrated into pMDI development programmes,

Drum lab

especially for reformulations using greener HFA 152a propellants. While traditional mixing vessels may still be employed for commercial production, the handling of flammable propellants will be facilitated. For commercial-scale manufacturing, we are developing dedicated new lines and retrofitting existing lines to accommodate this filling approach. Both options are being actively explored by our customers.

4. This process has its main application in the pharmaceutical industry for pMDI manufacturing. Any prediction on how this manufacturing approach may be received by the different regulatory bodies?

The evaluation of this simplified pMDI manufacturing approach by regulatory bodies such as EMA and FDA are ongoing. However, from our perspective, this dual-stage direct powder filling process appears straightforward and closely resembles current developmental practices. Therefore, we anticipate that transitioning to this new manufacturing process will be relatively smooth. We are actively seeking feedback from regulatory agencies, which will guide us in designing customised commercial lines in collaboration with our clients.

To learn more about our two-stage direct powder filling manufacturing process for producing sustainable pMDIs, please contact: tony@pharmatecsolutionsltd.com or visit our website: https://pharmatecsolutionsltd.com