



INHALATION MANUFACTURING: COLD FILL, PRESSURE FILL, AND FINDING THE RIGHT PARTNER

In this article, Mr Ross Errington, Business Development Manager, 3M Drug Delivery Systems, explains two pMDI canister filling methods – cold filling and pressure filling. He describes how each method can be applied to meet different formulation requirements, and outlines considerations for pharma companies when selecting an MDI manufacturer.

Both cold-fill and pressure-fill manufacturing methods for pressurised metered-dose inhalers (pMDIs) have existed for quite some time. When considering which route to pursue, pharmaceutical executives should understand the differences between these methods and how they lend themselves to various formulations. Pharmaceutical companies should also be aware of the capabilities they should consider when selecting a manu-

facturing partner. Finding the right manufacturing partner for an inhalation product can make the difference between a smooth and efficient development process versus one that is expensive and time consuming. Therefore, it is vital to understand the fundamentals of each technology and to examine what a manufacturer has to offer in each.

primary propellant in pMDIs is a gas at room temperature; therefore in order to formulate the product, the manufacturer must make that gas a liquid. The process begins with creating a concentrate with the active pharmaceutical ingredient (API) with a solvent or carrier that is a liquid at room temperature. These two components are mixed to form either a homogeneous suspension or a solution. In parallel, the bulk propellant, which forms the rest of the formulation, is placed into a pre-chilled vessel; the low temperature ensuring the propellant is in liquid form in the batching vessel. The concentrate is then transferred into the bulk-manufacturing vessel and the entire formulation is mixed. Therefore, a batching vessel will have a formulation

containing propellant, solvent/carrier, and the active ingredient, which can either be in solution or as a suspension.

The next step of the cold filling process is to dispense the formulation into appropriate sized canisters. This is achieved by pumping the formulation to a filling head and feeding a predetermined portion of the chilled liquid formulation into an open canister. A valve is placed on top of each canister and then crimped into place. A seal is formed between the top of the canister and a rubber component within the valve. Each completed pMDI is then checked

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UNDERSTANDING COLD FILLING

Cold fill is a method of manufacture in which cold temperatures are used to convert the drug formulation to a liquid phase. The



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Figure 1: Example of a pressure fill manufacturing line.

for weight to ensure the correct amount of formulation is in the product.

Products may then be water bathed to ensure a proper seal has been formed and that there are no gaps through which the propellant may leak. In cold filling, the water bath also serves the purpose of warming the aerosol to room temperature. The formulation in the canister remains a liquid, due to the fact that it is under pressure. After this step the pMDIs will be 100% function tested before batch release testing and final packaging operations are performed.

UNDERSTANDING PRESSURE FILLING

In contrast to cold filling, the pressure fill process uses pressure instead of low temperature to condense the propellant. The propellant is held in a pressurised vessel in liquid form (see Figure 1), and the drug concentrate is typically made in the same way as it is with cold filling, with the API mixed with a solvent or carrier that is liquid at room temperature.

Pressure-fill manufacturing can follow two separate courses. In one, known as two-stage pressure filling, the drug concentrate is placed in an open canister. A valve is then placed on top of the canister and crimped into position to form the seal. The propellant is then driven under pressure backwards through the valve and into the canister. Using this method, the mixing of the concentrate and propellant actually happens in the canister rather than in a bulk formulation tank. In common with the cold-fill process, after this step the unit is checked, weighed, water bathed and submitted for further processing.

The other method of pressure-fill manufacturing is referred to as single-stage pressure filling. In this process, the API and propellant are mixed and held under pressure. An empty canister is then fed onto the filling table and a valve is placed on top and crimped into place. The complete formulation is then fired under pressure into the canister. Following this step, the product is processed similarly to the other methods described.

Pressure Fill		Cold Fill
Single Stage	Two Stage	
<ul style="list-style-type: none"> • Solution with API that easily dissolves in an ethanol/propellant formulation 	<ul style="list-style-type: none"> • Typical suspension formulations 	<ul style="list-style-type: none"> • Thicker powder loading suspensions • APIs in which the particle size must be closely controlled during formulation
<ul style="list-style-type: none"> • Certain suspensions with very low powder loading and a very small amount of drug relative to the formulation 		

Figure 2: Criteria to consider when determining the match for a product.

Both two-stage and single-stage pressure filling rely on a step in which material is driven backwards through the valve, as opposed to the normal patient-use operation in which the valve opens to allow formulation out of the canister. It is therefore important in this filling process for the manufacturer to ensure they are re-sealed in order to prevent the product from escaping after filling.

ADVANCES IN TECHNOLOGY

There was a time when the equipment used in filling pMDIs was only capable of filling one canister at a time, during a process that was manually controlled and which required many manual checks. Today's pMDI filling lines utilise technology that allows the filling of multiple canisters at once, with electronic controls added to manage the filling process, rather than relying on manual intervention. With recipe-driven operating systems, electronic data generation, and the elimination of steps that require manual control, manufacturers are now able to deliver products that are more precise and more cost effective.

DETERMINING THE MATCH FOR A PRODUCT

Both pressure-fill and cold-fill manufacturing methods were developed several decades ago. In today's market, pressure filling is the most prevalent in the manufacturing industry. However, certain formulations of drugs actually lend themselves better to cold filling than pressure filling operations. In order to determine which method of manufacturing to pursue, pharmaceutical companies should examine the properties of their formulations (Figure 2).

A formulation that is a solution, which has an active ingredient that easily dissolves in a solvent/propellant formulation, is ideal for single-stage pressure filling, due to the fact that it can very simply be driven as a liquid backwards through the valve on the canister. Single-stage pressure filling can also be appropriate

for certain suspensions that have particularly low powder loading – a small amount of drug relative to formulation as is sometimes found in high potency products.

Two-stage pressure filling is nearly always used with a typical suspension formulation, in which the drug loading of the formulation is too thick for it to be dispensed into the can through the valve with repeatable accuracy.

In the cold-fill process, there are fewer concerns as to whether the formulation is a solution, or a low powder loading or thick powder loading suspension. Cold filling does lend itself very well to thick powder loading suspensions, in that the fully suspended formulation is created in the vessel and the manufacturer is not reliant on the propellant and the concentrate mixing properly in the small canister. For this type of formulation, cold filling is typically preferable to two-stage pressure filling, in which the proper mixing is sometimes not achieved within the canister. Incomplete mixing can prevent a homogenous suspension from being formed and cause inconsistencies in testing.

Cold filling also makes more sense for certain APIs in which the manufacturer seeks to control the particle size closely. With a cold fill process, the chilling of the concentrate can be used to control the crystallisation of the product and therefore the particle size.

WHAT TO LOOK FOR IN A MANUFACTURER

Whether seeking a manufacturer with cold fill, pressure fill or both capabilities, pharmaceutical companies should ask themselves if they need purely a manufacturer, or a manufacturer that provides additional services such as on-site development, access to analytical testing, and regulatory support. In either case, a manufacturer should have a significant track record of inhalation production, preferably with the type of drug in question.

Additionally, a manufacturer should be able to give examples of many different types of formulations it has worked with. As drug com-



Figure 3: MDI components.

ination products increase in popularity, a broad track record will become even more important.

Pharmaceutical companies should consider what a manufacturer's track record consists of and how robust it is, as these factors can help maintain manufacturability over the product's

lifetime (see Figure 3). To keep the product's development timeline ahead of competitors, a manufacturer should have the ability to scale-up production quickly from development through commercialisation. At the same time, the manufacturer must be able to meet regulatory require-

ments and adhere to current good manufacturing practices (cGMP).

The ability to offer guidance in the patent process is another quality that a strong manufacturing partner can offer. Navigating existing patents and finding ways to combine drugs for new patents takes innovation and expertise. In addition, a robust market presence and supply chain are vital. Having manufacturing sites around the world can help increase flexibility and prevent supply issues in critical areas.

As we know, the challenges in the pharmaceutical industry are far from standard, and pharmaceutical companies need partners that have a wide range of tools to meet these challenges. In order to set products up for success, companies should look for manufacturers that have extensive expertise, from the pilot stage to full-scale production. Wide-ranging expertise and long-term experience can go far in helping new inhaler products achieve a successful launch, whether they are pressure-fill or cold-fill devices.

By working with a manufacturer that has experience developing and manufacturing both types of product, as well as expertise in the development and manufacturing process from start to finish, pharmaceutical companies can give themselves an advantage over the competition.



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