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Review Article

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Pressurized Metered Dose Inhaler Technology: Manufacturing

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Abstract. While first introduced in the 1950s, pressurized metered dose inhalers (pMDIs) remain as a first line treatment of pulmonary conditions. With expanding applications of pMDIs beyond asthma and chronic obstructive pulmonary disease (COPD), the development of therapies utilizing the pMDI platform will undoubtedly continue. Recent guidances and the introduction of quality by design initiatives further emphasize the requirement of formulators to understand the relationships between product attributes and production strategies and their impact on product performance. This review summarizes common manufacturing processes of pMDIs across multiple stages of the development cycle, from academia to commercial production, and provides insight as to the benefits and limitations of each process in regard to formulation type.

KEY WORDS: manufacturing; pressurized metered dose inhaler (pMDI); critical quality attribute (CQA); cold filling; pressure filling.

INTRODUCTION

The pressurized metered dose inhaler (pMDI), since its introduction in the 1950s, is now well established as a primary means of treating asthma and chronic obstructive pulmonary disease (1). While the first manufacturing processes relied on existing means of packaging aerosols (2), new techniques have evolved to address the specific difficulties in the manufacture of pMDIs, such as their relatively small container volume and the limitations of the metering valve such as the pressure required to back-fill through the valve (1). Today, the techniques used to manufacturer pMDIs vary extensively based on formulation requirements, critical process parameters, and the limited resources of the manufacturer in regard to capital and expertise. In practice, these variations can be distilled down into two major processes, characterized by the way in which the currently used hydrofluoroalkane (HFA) propellants are liquefied: cold filling and pressure filling (3). Additionally, each process has specific technical modifications and considerations whether manufacturing solution or suspension formulations (4). Recent guidance from health authorities and the introduction of quality by design initiatives further emphasize the requirement of formulators to understand the relationships between product attributes and production strategies and their impact on product performance (5–8). This review intends to outline each manufacturing process from initial combining of raw materials to final product filling, for the purpose of making an informed decision on selection and considerations for the pMDI manufacturing process.

GENERAL CONSIDERATIONS

Broadly, the pMDI manufacturing process involves combining the formulations components in bulk (*i.e.*, batching), followed by dispensing (*i.e.*, filling) that material into a container. During batching, it is especially critical to accurately and properly dispense the material as this ratio will determine the concentrations of the active pharmaceutical ingredient(s) (API) and excipient(s) in the finished product (9). This process is complicated by the inclusion of a volatile propellant, either 1,1,1,2-tetrafluoroethane (HFA-134a, also called norflurane) or 1,1,1,2,3,3,3-heptafluoropropane (HFA-227ea, also called apaflurane). Under normal working pressures, these propellants are liquefied gases and maintain a constant vapor pressure at a given temperature regardless of container volume, eliminating the effectiveness of traditional means of determining vessel fill level or leakage by pressure change (10). Weighing of the batching vessel and product is the standard for determining leakage and fill level during production (11).

The handling of the propellant requires careful consideration. Propellant in the vapor phase that may be trapped in

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pumps or filling lines can pose a safety concern, impede mass flow, and lead to inaccurate dispensing (12). This is especially the case in setups with significant dead volume, for example, where feed lines and equipment are too large for the batch size or are mis-sized as the batch empties causing a greater portion of the propellant to transition to the vapor phase. Additionally, to access the liquid phase for uniform dispensing and pumping, the orientation of the container and location of sampling is important. For instance, a valve on the top of a batch vessel will only sample from the vapor phase, whereas a dip tube would primarily sample from the liquid phase until the vessel is almost empty. The vapor pressure of the bulk formulation is also sensitive to temperature, as discussed in "Cold Filling," as well as cosolvent concentration. The reduction in vapor pressure upon chilling or propellant addition can result in a formulation which no longer adequately feeds subsequent pumping and filling equipment and additional elements which are necessary to ensure adequate process performance.

In evaluating a new formulation for manufacture**,** one of the first aspects to account for is the purity and cleanliness of the packaging components and raw materials. Primary packaging should be cleaned to ensure the absence of any contaminants such as fabrication aids, packaging material, or undue microbes (5,8,11,13). For instance, uncoated aluminum canisters may rub and flake during shipment and storage. Formulation components additionally require care. Apart from effects on product performance, particulates in the formulation media can have disastrous effects on manufacturing equipment. For example, the flaking of iron particles from a propellant cylinder can scratch the metal and/or damage elastomers of the pump head of a pressure filling system. As a result, all fluids should be filtered using a membrane filter with a pore size of 0.2 μm or smaller before addition and where suitable (*e.g.*, not suspension formulations), filtered immediately prior to filling (13).

Depending on the nature of the API as well as the physical and chemical properties of the formulation, varying amounts of environmental control are also necessary. The most common of these is humidity control, both in dealing with hygroscopic formulations and during cold filling of sensitive formulations, where additional humidity would cause condensation or ice formation on chilled manufacturing equipment or packaging components promoting moisture ingress (3,5,7,8). The added moisture can affect formulation stability if any component is susceptible to degradation by hydrolysis (10). Propellants are susceptible to water absorption to a finite extent and indeed all propellants contain trace amounts of water; however, the solubility of water in propellant can be significantly increased based on the nature and concentration of excipients added (14). The choice of propellant itself can have an impact on moisture content with nearly a fourfold increase in the solubility of water for HFA-134a (2220 ppm at 25°C) compared to HFA-227ea (610 ppm at 25°C) (15).

FILLING

Present practice, both in industry and academia, for the filling of pMDIs with the desired formulation can be divided into four common procedures; some of the advantages and disadvantages of each are included in Table I. Volatile component handling can be divided into pressure filling, whereby the volatile portion is filled into the canister through the metering valve under pressure, and cold filling, whereby the volatile portion is chilled and filled into an open canister at room temperature. Both procedures can be carried out with either in a single stage, in which the entirety of the formulation components are premixed and added to the canister in a single step, or in two stages, also referred to as concentrate addition or two-step filling, in which an aliquot of non-volatile formulation is added to the canister first followed by the volatile portion. The following sections linearly describe the processes for each of the aforementioned filling methods.

Pressure Filling

Currently, pressure filling is the most common procedure utilized by industry. The methods for single and two-stage filling rely on maintaining the system at a sufficient pressure to render the volatile propellant a liquid and driving that liquid propellant or bulk formulation through the metering valve into a previously crimped and sealed canister. Since this is the opposite of the normal flow of formulation through the valve during use of the pMDI, it is of the utmost importance to ensure that the valve is re-sealed following the pressurized filling (16). The popularity for this manufacturing process stems from operational advantages over a cold filling system (17). For example, it is less costly to maintain pressure as compared to the precise control of temperature required for cold filling and exposes the product to fewer fluctuations in temperature and pressure outside of a closed system (18).

Single-Stage Pressure Filling

Single-stage filling involves the dispensing of a formulation containing the API(s) along with any excipient and the propellant in a single action into the primary packaging, usually composed of a crimped canister with metering valve. The order of addition of formulation ingredients can be extremely important in preparing a successful formulation. For example, if during batching, an API is added to the batch vessel containing an excipient in which the API is partially or completely soluble, but where the API is not freely soluble in the final formulation, it is likely that the primary particle size of the API will increase or the formulation will precipitate (11). This could drastically affect both immediate drug product aerodynamic performance and long-term physical stability. However, mixing the propellant and all excipients followed by adding the API using a separate vessel reduces the likelihood of Ostwald ripening (19). While single-stage pressure filling is still an option for suspension formulations, along with maintaining homogeneity (20), an additional critical factor is the suspended particle load. Relatively high suspended drug concentrations may cause the filling head or metering valve to clog and not properly reseal following filling (16,21). As a result of these concerns, the single-step process is most ideal for formulations in which the active ingredients are fully soluble in the excipient and propellant mixture or for dilute suspension formulations (11,16).

Table I. Filling Process Key Attributes

	Single-stage		Two-stage	
	Advantages	Disadvantages	Advantages	Disadvantages
Pressure filling	• High efficiency • Solution formulations • Some dilute suspensions • Canister is sealed during filling • Tighter tolerances	• High powder load suspensions • Propellant loss to vapor	• Limited waste of API • Can be low cost setup • Many solution formulations • High powder load suspensions	• Wider tolerances • Propellant loss to vapor • Concentrate mixing for suspensions • Difficult scale-up • Mixing for suspensions
Cold filling	• High efficiency • Many solution formulations • Many suspension formulations • Suspensions with API that is soluble in concentrate of excipient • Tighter tolerances	• Drug solubility at low temperature • Phase separation at low temperature • Environmental controls	• Limited waste of API • Can be low cost setup • Many solution formulations • Many suspension formulations • High powder load formulations	• Environmental controls • Antisolvent effects • Widest tolerances • Difficult scale-up • Canister open for long period of time • Can be a slower process • Mixing for suspensions

The process for single-stage pressure filling first starts with bringing the metering valve into communion with the canister and crimping the valve-canister assembly to form the primary packaging. Concomitant with this step is the purging of atmospheric air from the canister, which is intended to eliminate any water, oxygen, or particulates from the container, preventing contamination or degradation of the final product and minimizing internal canister pressure so that it will not deform when filled (18,22). Without removal, the atmospheric air trapped in the canister would increase in pressure, following Boyle's law, as the liquid formulation is added and reduces the available volume of the canister, which could cause it to deform or burst. This is important as the single-step pressure filling process does not "self-purge" due to the pressurized addition of all formulation components into a sealed system (18).

Purging air from the canister can be carried out by specialized equipment which imparts a vacuum on the canister immediately prior to crimping or "self-purged" through the addition of a small amount of liquefied propellant to the empty canister. The resulting propellant flashing and density of propellant relative to air displaces the air in the canister, which is then crimped (3,22). While displacement is advantageous for small-scale setups due to the prohibitive cost of vacuum-crimp systems, using a separate propellant addition and flashing steps prior to crimping slows the process and reduces output as well as lacks the level of process control as a vacuum-crimp system (18).

Following the preparation of the canister and valve, the two components must be crimped together in order to form the sealed primary packaging (*i.e.*, container closure system) prior to filling the system with pressurized formulation. This is accomplished, as depicted in Fig. 1 by applying both vertical and radial pressure to the metering valve, compressing the sealing gasket while also forming the "crimp" which holds the valve and canister together (23). The figure also details some important considerations such as a properly fitted depth stop and crimp collet, which are specific to the canister and metering valve combination.

The container closure system is then ready to be filled. Figure 2 shows a potential equipment setup for either suspension or solution filling. For both suspension and solution formulations, the bulk will be under constant mixing and held at a pressure suitable to keep the propellant liquefied. Continuous mixing within the batch vessel is considerably more important for suspension formulations than solution formulations due to the risk of separation of the suspended particles from the remainder of the formulation to the detriment of total can drug content which impacts dosage uniformity and aerodynamic particle size distribution (16,24). However, for ease of adapting manufacturing setup for suspension formulations to solution formulations or scaling up the manufacturing process, it is still common practice to mix solution formulations throughout the manufacturing process and attempt to match the number of batch turnovers (*e.g.*, in the instances of in-line homogenizing or recirculation prior to filling) across various manufacturing scales (16).

Once ready to be filled, the filling equipment utilizes a very high pressure, generally an injection pressure between 50 and 80 bar based on the valve manufacture's specifications, to drive the bulk material into the container through the valve (12). The vapor pressure of the formulation alone is not sufficient to supply this pressure and relies on a series of pumps; for instance, the Pamasol diaphragm filler requires between 10 and 12 bar supply pressure, generated by a recirculating diaphragm pump, as depicted in Fig. 2. The high-pressure single-stage filling is specifically advantageous for formulations with suitably low concentrations of API. The comparably large volume dispensed in a single step reduces variability caused by inaccurate amounts of drug or excipient dispensing into the container, either due to inaccurate low volume metering or substantial amounts of material being left on the filling head or valve stem, which can occur with two-stage filling (25,26).

During this process, it remains especially important to keep suspension formulations constantly recirculating and mixing to avoid vapor lock formation or settling or creaming of suspension in the pump lines or filling head (27). This can be aided by keeping the formulation cooled, around 5°C, to

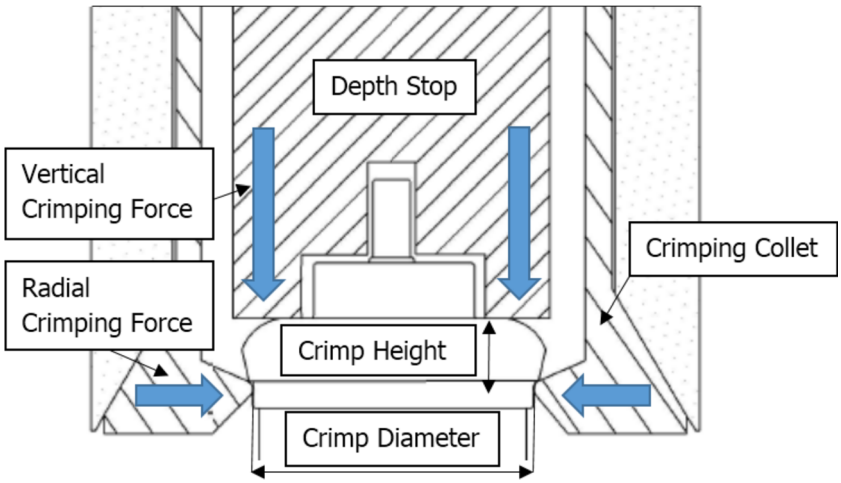

Fig. 1. Schematic of crimping head and parameters to consider for crimping. Adapted from Hickey A. Pharmaceutical Inhalation Aerosol Technology. 2 ed.: CRC Press; 2004

prevent a vapor lock in the feed lines and metering cylinder of the filler caused by slow evaporation of the propellant (12), so long as cooling does not result in precipitation of any drug or excipient. Maintaining a constant batch temperature also improves formulation dispensing accuracy as it allows for a stable formulation density and thus the amount of formulation dispensed by volume is more repeatable. Additionally, it should be considered that the constant vapor pressure maintained by the propellant leads to a gradual propellant loss to the headspace of the mixing vessel as the batch is filled which can lead to an increased API concentration at the end of filling a batch, accounting for upwards of 30% loss due to product that goes unfilled or falls outside of acceptable tolerance ranges (28). In-line measurement of API concentration in combination with a propellant top-off system and simple modeling provides sufficient control over the propellant loss and aids in batch end repeatability (28,29). Propellant top-off systems can include real time monitoring of API concentration and automated addition of propellant or can be pre-determined amounts of propellant added once, or multiple times, at a set batch volume or weight of bulk remaining. By precisely adding the correct volume of propellant, the concentrating effect of the loss of propellant can be offset. Having a firm understanding of the effects of vessel size on batch behavior throughout filling will help facilitate scale-up and transfer between different vessel sizes.

Two-Stage Pressure Filling

Much like single-stage pressure filling, two-stage filling utilizes higher than atmospheric pressure to maintain the propellant in a liquid state. Unlike the single-stage process,

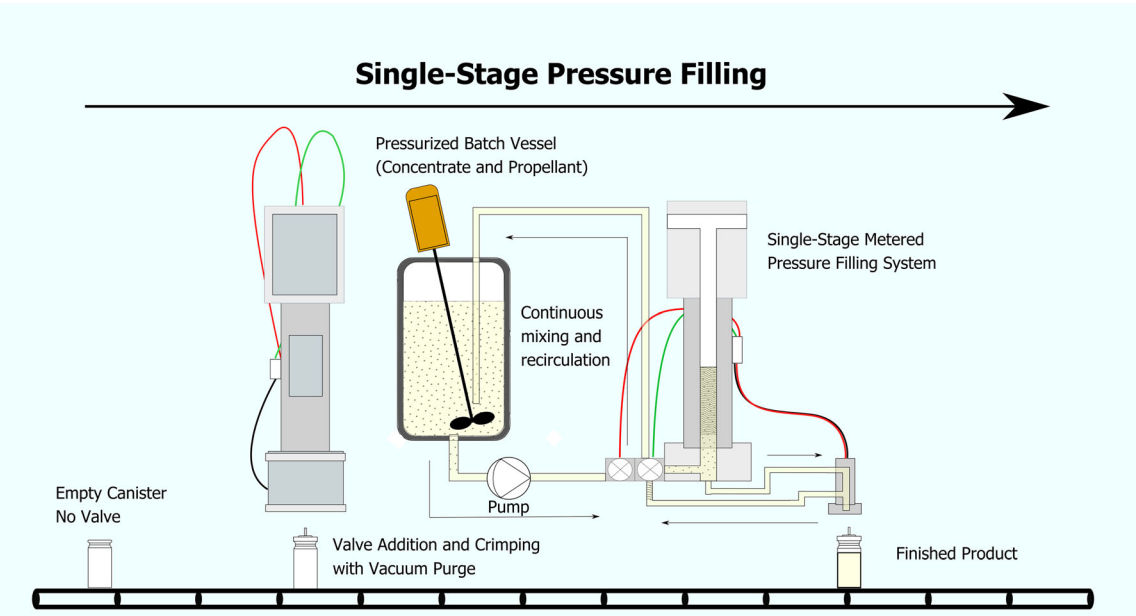

Fig. 2. Possible setup for single-stage pressure filling pMDI manufacturing process. The canister is first purged of air and crimped followed by pressurized filling through the valve. Note that the order of addition and homogenization of the bulk formulation is not shown

batching for two-stage pressure filling involves combining the API with some or all of the nonvolatile excipients to form a concentrate which can be dispensed into the open canister. In terms of formulation selection, two-stage filling is more suited for formulations where the drug and excipients are readily soluble in the final formulation, rather than suspensions where mixing with excipients alone can partially or completely dissolve the API (12). On the other extreme, this process can be suited for use with suspension formulations in which there is a high concentration of suspended ingredient, to the point that the formulation is too viscous to be dispensed through the metering valve of a single-stage pressure filler with repeatable accuracy (16). This process is also preferred in drug development programs where the available amount of API and small number of required product units make large volume batching uneconomical. However, as there are multiple instances of filling, the error from each of those steps is stacked leading to an increased in possible variability compared to single-stage pressure filling.

Figure 3 depicts a possible concentrate filling equipment setup. Since the container closure system is not self-purging, clearing of the headspace of the canister must occur prior to crimping similar to the single-stage process. Vacuum-crimp system is not suitable however, since the canister will contain some amount of concentrate at the time of the valve is attached, thus purging the canister using small quantity of propellant/gas prior to the addition of concentrate must be used (12). In the specific case where the concentrate contains a volatile, heavier than air component the process can then be considered self-purging as the volatile ingredient displaces the air upon the addition of the concentrate (18). As the canister will remain open to the environment following the propellant purge, it is critical to maintain a clean and dry environment to prevent the ingress of particulates, moisture, or microbes during concentrate addition (13).

Following purging of the canister, the concentrate is added and the canister and valve are crimped. If any ingredient in the concentrate is volatile, it is common to chill the concentrate slightly below ambient temperature as a means of preventing loss of excipients due to evaporation (13). Large and even pilot scale equipment for the volumetric filling of concentrates exists and has an action similar to that of a syringe plunger, which is operated pneumatically. However, such equipment is not a requirement for bench scale production; any sufficiently accurate dispensing system is suitable (12).

Once the concentrate is added and the primary packaging is sealed, the container is charged with the desired propellant(s), commonly referred to as gassing, which can be carried out by high speed fillers (12). Of the four processes discussed within this review, two-stage pressure filling can be the least costly to setup as propellant can be charged directly from its cylinder, although use of a pressure burette is recommended, and no expensive chilling or pumping equipment is required. There are, however, a greater number of potential risks which may affect the performance of the final product, not to mention significant difficulty scaling up from such a setup. For instance, the rapid change in the drug solution or suspension environment upon the addition of HFA can be detrimental to the formulation. If the concentrate was a solution, the rapid addition of propellant can cause drug to precipitate. While this has been used intentionally to produce suspensions *in situ* (30,31), there is significant risk of crystal growth and formulation failure if precipitation is not identified or extremely well controlled. Further, the interconversion of metastable crystal forms has been shown to be possible when the concentrate is exposed to specific environmental conditions both with and without propellant (32,33). Mitigating these risks, especially in a regulated environment, requires a more involved process considering the multiple errors that compound for each step.

Additionally, unlike the single-stage process in which the bulk formulation is capable of being mixed and/or homogenized at its final concentration, there is little ability to process

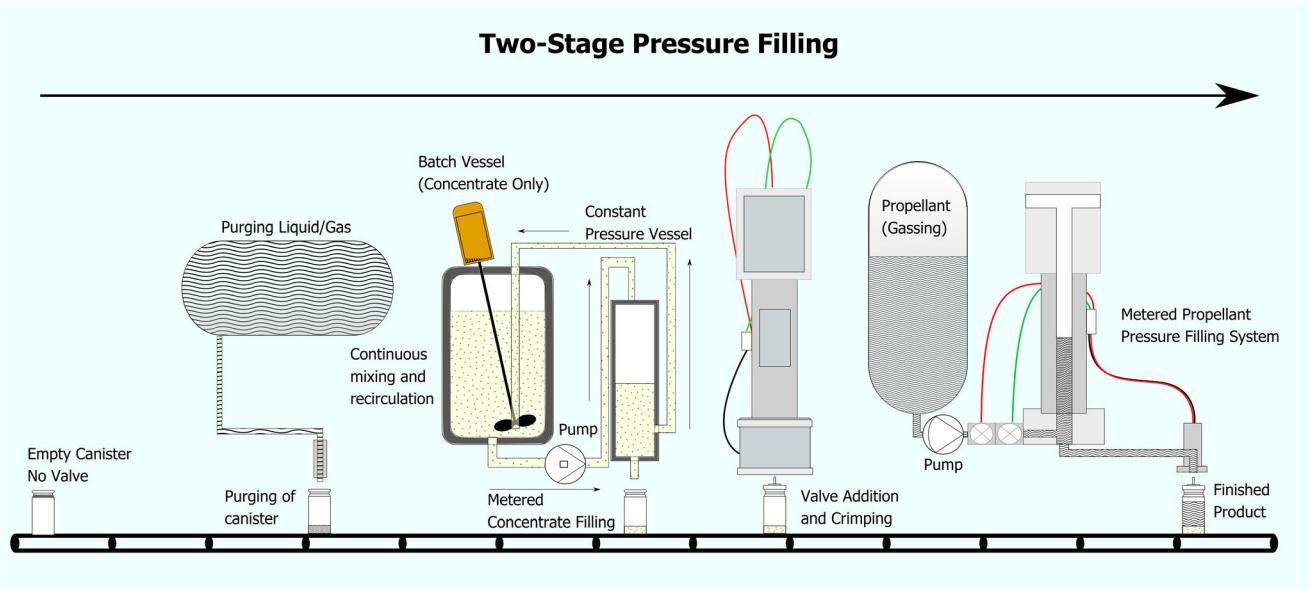

Fig. 3. Possible setup for two-stage pressure filling pMDI manufacturing process. The canister is first purged of air by propellant/gas addition followed by dispensing of the API and excipient concentrate. A valve is attached and the container is filled with propellant. In this setup, the process depicts gassing with propellant only; however, this could be either a mixture of propellants or propellant(s) plus excipient(s)

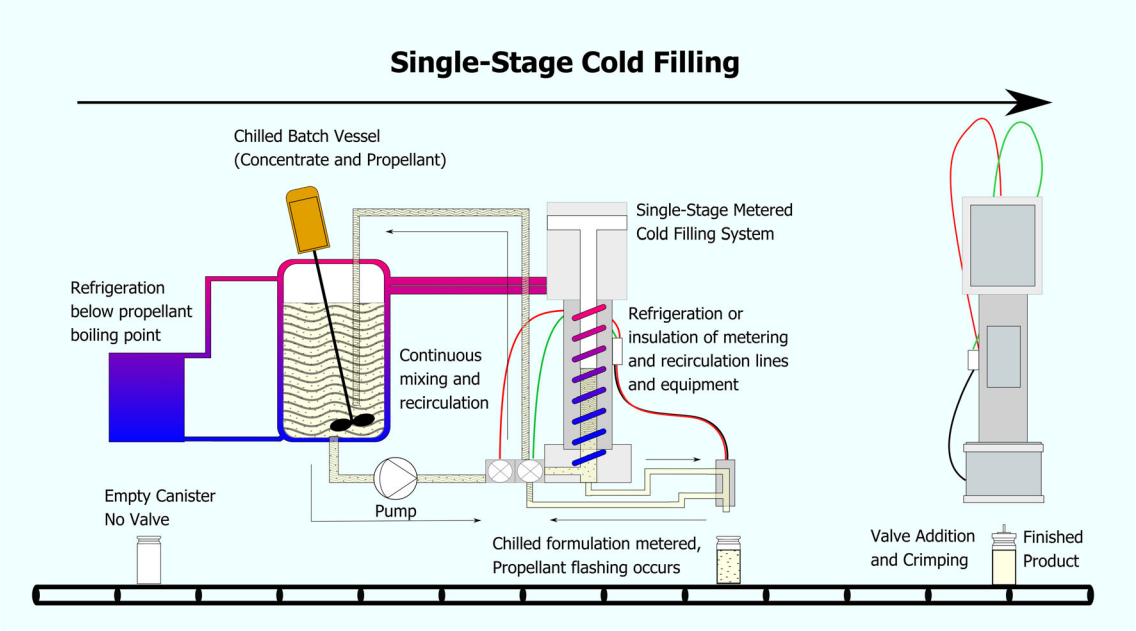

Fig. 4. Possible setup for single-stage cold filling pMDI manufacturing process. The chilled formulation is dispensed into an empty canister which is self-purging. The valve is then crimped on the canister. Note that the order of addition and homogenization of the formulation bulk is not shown

the final formulation with two-stage pressure filling as the mixing occurs in the canister under the force of the propellant addition rather than in the batch vessel (34). This can be especially concerning when dealing with difficult to deaggregate or disperse suspensions (16). The concentrate is capable of being homogenized prior to dispensing into the canister; however, this is still less ideal than homogenization of the complete bulk formulation. Limited post-filling deaggregation has been accomplished *via* sonication (35); however, this requires evaluation on a formulation by formulation basis as not all suspensions will homogenize or respond well to the heat generated by sonication (36).

For the two-stage filling process, it is necessary to accurately meter, on a per unit basis, both the concentrate and the propellant in order to produce a final product with the correct formulation concentrations. The requirement for highly accurate and reproducible small volume dispensing is something that can be especially challenging with suspended products in which drug particles inconsistently adhere to the concentrate dispensing surfaces (25,26). This risk results in recommended individual weight checking each unit at both stages to ensure conformance (13,18) which can lead to a slower and/or more expensive process overall. As a result, this technique most benefits smaller-scale operations.

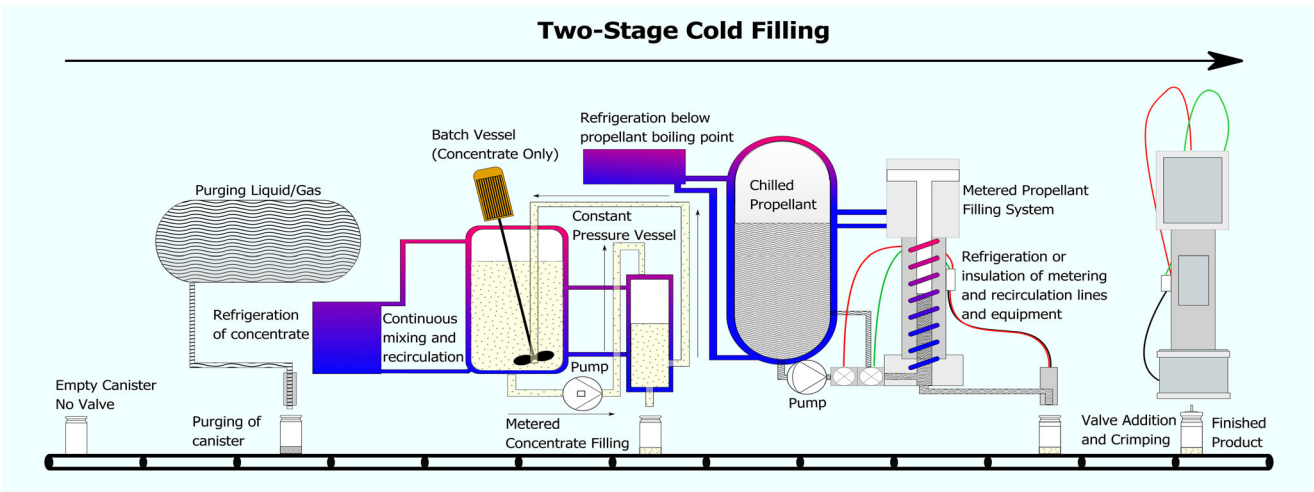

Fig. 5. Possible setup for two-stage cold filling pMDI manufacturing process. The empty canister is purged of air by propellant/gas addition followed by dispensing of the concentrate mixture. The concentrate may be a mixture of excipients and API or the API alone. While chilling is not required as there is no highly volatile component, maintaining the concentrate filling at or near the temperature of the chilled propellant reduces the likelihood of excessive flashing and formulation loss upon addition of the liquid propellant. The propellant is added and valve crimped in place

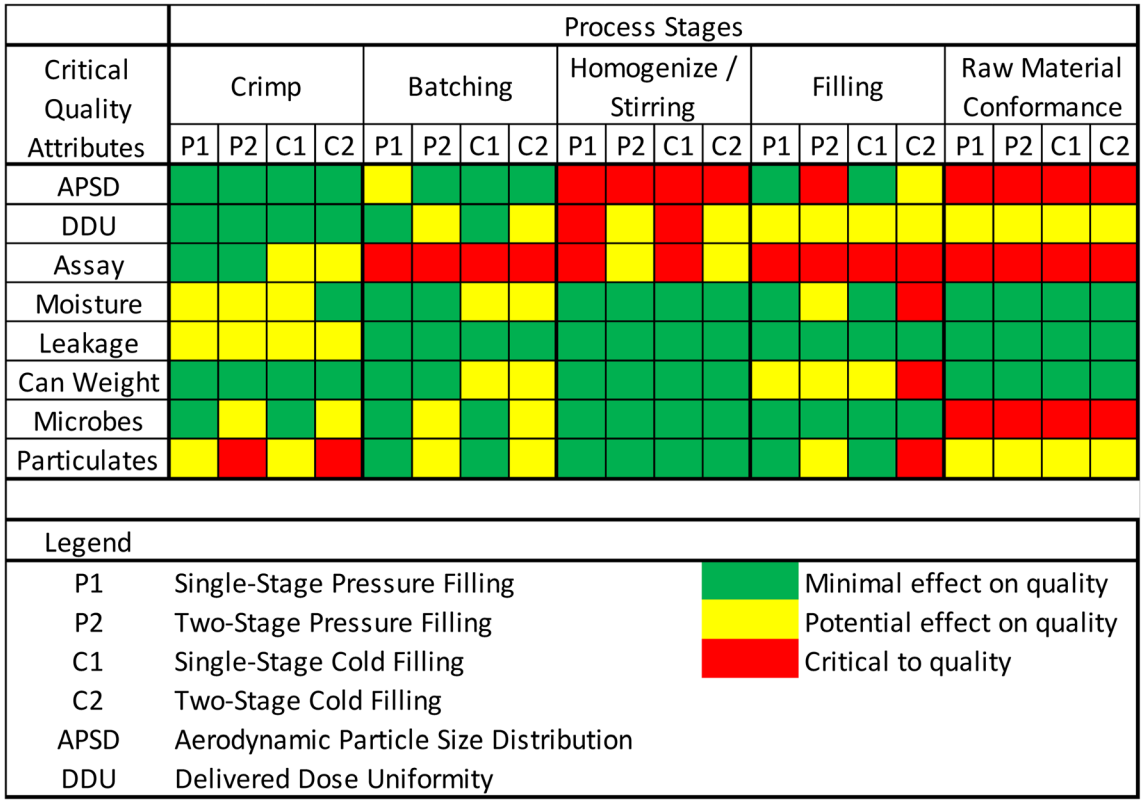

Fig. 6. Manufacturing process stages that may affect drug product critical quality attributes depending on the filling method employed. The increased criticality of stages indicates that greater understanding and validation of the specific stage is required to ensure product conformance and batch repeatability

Cold Filling

Prior to the development of the technology required for pressure filling, the manufacture of pMDIs was carried out by cold filling, facilitated by one of the chlorofluorocarbon propellants (trichlorofluoromethane, known as CFC-11) being a liquid a room temperature (15). Cold filling is a process by which the propellant is maintained as a liquid at atmospheric pressure using temperatures that are sufficiently low (17,25). While no longer the most common for new commercial production, the versatility and ease of use of cold filling has allowed it to maintain its value with early-stage formulation development and with specific formulations (16). Although many of the general steps for single and two-stage cold filling are the same as their respective pressure filling processes, cold filling processes have some limitations. Cold filling is especially susceptible to moisture and particulate uptake during crimping due to condensation of water or ice formation from the atmospheric air onto the chilled components of the filling equipment or packaging components (18,25), a risk which modern commercial processes reduce through environmental controls at the point of filling. Additionally, formulations which have a tendency to separate into two or more liquid phases upon significant cooling are not suitable for cold filling (17,37).

Single-Stage Cold Filling

The first step in cold filling is the preparation of the API with excipients. Processes may utilize an excipient and/or propellant that is liquid at ambient temperature and pressure, such as ethanol, to form a concentrate solution or slurry of suspended drug (25). Alternatively, the process might employ a pressurized addition of propellant to the API prior to chilling the formulation or pre-chill the propellant before adding the concentrate (16,17,38). Once the formulation contains all the required components, it must be sufficiently mixed and/or homogenized. In the case that extensive homogenization is required, care must be taken to ensure that the heat generated from homogenization does not cause the liquefied propellant to vaporize or substantially increase the solubility of the API.

The equipment setup for cold filling is represented by Fig. 4. Cold filling for the single-step process differs from its pressure filling equivalent in that the predetermined portion of the cooled liquid formulation is dispensed into an open canister, which necessitates significantly greater effort to control the ambient environment and the time required to fill (16). Maintaining adequate circulation and filling pressure is also a concern, as the chilling of the propellant reduces its vapor pressure well below the inlet pressure required by many pumps and fillers to accurately dispense formulation into the canister. As a result, it is common to maintain a compressed gas headspace, usually dried air or nitrogen, as a means of supplying pressure or by multiple pumps in series to scale system pressure (12). Care must be taken, additionally, that the effect of the dissolved headspace gas in the propellant is well understood as it has been shown to effect aerosol generation as the partial pressure of the gas contributes to the canister pressure of the pMDI (21,39,40).

Table II. Potential Causes for Poor Performance from Manufacturing Process Stage

Critical quality attributes	Manufacturing process stages	Examples of potential causes for poor performance
Aerodynamic particle size distribution (APSD)	Batching	• Solubility in excipient, agglomerate formation, mixing order for suspensions
	Homogenize/stirring	• Ineffective homogenization/stirring, settling or creaming occurs, milling of suspended product • Heat generation may increase solubility or degrade sensitive compounds
	Filling	• Relative proportion of drug to excipients affects aerosol generation
	Raw material conformance	• Input particle size affects aerodynamic performance of suspensions
Delivered dose uniformity (DDU)	Batching	• Solubility in excipient, higher variability in concentrate filling
	Homogenize/stirring	• Insufficient mixing/homogenization of the bulk
	Filling	• Relative proportion of drug to excipients affects delivered dose
	Raw material conformance	• Input particle size affects aerodynamic performance of suspensions
Total canister content assay	Crimp	• Evaporation of volatile excipients or drug, excessive flashing
	Batching	• Inaccurate addition of excipient or drug due to transfer loss or inaccurate measurement • Adhesion to surface of transfer vessels
	Homogenize/stirring	• Incomplete solubility/deaggregation of the bulk • Evaporation of volatile excipient or drug • Suspension formulation settling • Incomplete dissolution of excipients or drug
	Filling	• Concentrating affect due to evaporation of propellant into head space of batching vessel • Deposition of suspended drug in filling line, head or metering valve
	Raw material conformance	• Purity of raw material or excipient • Correct crystal/salt form of material or excipient
Moisture	Crimp	• Moisture ingress due to poor crimp • High ambient humidity at time of crimping • Failure to purge ambient air from canister
	Batching	• Failure to purge ambient air from the vessel • Condensation formation due to transfer of chilled formulation or concentrate
	Filling	• API/excipient adsorbing moisture from ambient air • Condensation formation due to transfer of chilled formulation or concentrate into open canister
Leakage	Crimp	• Over or under compression of gasket may increase leakage • Selection of gasket has impact on permeability of vapor • Gasket incompatible with chosen excipients
Can fill weight	Batching	• Physical property changes of propellant/excipient • Liquid phase separation
	Filling	• Inaccurate filler setting • Pressure fluctuation in feed line • Excessive flashing • Compounding errors from two-stage filling
Microbes	Crimp	• Can exposed to environment • Lack of proper cleaning • Inadequate purging of ambient air • Lack of environmental controls
	Batching	• Residual moisture/contaminants in vessels • Lack of proper cleaning • Exposure of concentrate
	Raw material conformance	• Contamination of raw materials
Particulates	Crimp	• Can exposed to environment • Lack of proper cleaning • Inadequate purging of ambient air • Lack of environmental controls
	Batching	• Residual moisture/contaminants in vessels • Lack of proper cleaning • Exposure of concentrate
	Filling	• Lack of proper cleaning of components • Can exposed to environment
	Raw material conformance	• Particulates in raw materials • Propellant not filtered

This table only provides potential causes of poor performance for those indicated in red or yellow in Fig. 6

The crimping process for cold filling is essentially the same as for pressure filling except that the process during cold filling is substantially more time sensitive as the propellant starts to quickly warm to ambient temperature. Single-stage cold filling is the only self-purging process as the flashing of a small amount of cold propellant, when dispensed into the room temperature canister, displaces the air in the headspace of the canister removing the need for an additional vacuum or propellant purging step (18). If this flashing of propellant is violent, or there are issues with product reproducibility, the formulation temperature should be further decreased or the canisters may be chilled to reduce the flashing and allow more time to transition between filling and crimping the metering valve in place (38) although chilling of canisters risks condensation without sufficient environmental controls.

Two-Stage Cold Filling

The two-stage cold filling process, with an independent propellant addition step, is favored by academia and for small-scale development batches. It is not routinely used for commercial manufacturing due to difficulty of scaling up this process. The advantages of two-stage cold filling compared to single-stage processes are the simplicity and affordability of the equipment and the ability to make extremely small numbers of canisters (even batches of only a single canister) with minimal wastage of API. Figure 5 depicts the equipment train for a larger scale production; however, the purpose and function remain the same regardless of scale of production.

Fundamentally, the two-stage cold filing process is similar to the two-stage pressure filling process. The canisters are purged of ambient air, followed by the addition of a concentrate of drug and excipients to the canisters. Deviating from the two-stage pressure fill process, the valve is not crimped in place until after filling with chilled propellant (41,42). The propellant addition, and subsequent propellant flashing, is of concern if the suspension product is formed due to antisolvent effects from the propellant (37). In addition, the exposure of the formulation to ambient conditions for extended amounts of time, longer than for either two-stage pressure filling or single-stage cold filling, significantly increases the chance of particulate or moisture ingress and variability in semi-volatile and volatile excipients concentrations due to evaporation of these species from the formulation concentrate. As with two-stage pressure filling, homogenization of suspensions can be particularly challenging, even more than with pressure filling, as there are far less shear dispersion forces upon addition of the chilled propellant (34). Post-filling sonication has been used successfully (42); however, it requires stability evaluation on a per-formulation basis.

IMPACT OF MANUFACTURING PROCESS ON PRODUCT PERFORMANCE

It is important to note that the process selected, and any manipulations of that process, may result in subtle differences in product performance. As a formulator, it is important to recognize what stages of the manufacturing process might impact critical quality attributes (CQA) of the product. Specific to the four main processes discussed, Fig. 6 identifies when and to what degree specific manufacturing processes and stages might impact the product. The figure indicates that certain process stages have the potential to critically impact one or more of the quality attributes (marked in red) and steps should be taken to control and verify that this process is occurring as expected. Table II provides some rationale for the ratings noted in Fig. 6. For example, when considering a suspension formulation using a two-stage pressure filling process, particular care must be taken when filling: that the amounts of concentrate and propellant are within tight tolerances and that there is sufficient deaggregation of the suspended particles—something that can be challenging with a two-stage process. Failure to control for these is likely to result in significant changes in product aerodynamic particle size distribution (APSD), delivered dose uniformity (DDU), and total canister content assay as imprecise filling can result in inaccurate API concentration, the particles can fail to deaggregate, or they can become unevenly disbursed during this process. Likewise, that same formulation manufactured using a single-stage pressure filling process will also have to pay close attention to the effects of homogenization; however, this process is able to impart greater control as the whole formulation can be homogenized together. Unlike two-stage batching, single-stage batching with this formulation would require greater care in the order of addition of excipients and API, as detailed in "Single-Stage Pressure Filling," or risks alterations of the primary particle size resulting in changes to product APSD. Filling also is less critical to APSD for the single-stage pressure fill as the entire formulation is filled in a single step; there can be limited changes to API concentration and particle distribution at this stage. This is not to say that filling is not critical, as imprecise filling can result in shorter product life and drop-off in delivered dose at the end of life, only that it will likely not result in significant changes to APSD.

Note that there can be process issues which, while not common or critical for the bench or pilot scale process, might be critical once that product has moved to a different manufacturing line for scaling to clinical or commercial levels. For instance, such may be the case when a suspension drug product which was initially formulated using two-stage pressure filling is moved to a single-stage pressure filling line. With this single-stage process, it will be of greater importance to understand and control homogenization and stirring to ensure proper mixing of the propellant with the formulation concentrate, something that may not have been a concern during two-stage filling where mixing was accomplished in the final product. Likewise, solution and suspension formulations will also have different exposure to potential risks, as is the case with homogenization and stirring where suspensions are much more sensitive. The result is that each new formulation must be considered at each stage of the manufacturing process for potential effects that would have a significant impact on the product quality and that sufficient process controls are put in place to mitigate these effects.

CONCLUSION

There is significant variance in each of the common pMDI manufacturing processes that a product-specific approach should be taken when selecting a manufacturing process. Single-stage pressure filling is the industry

commercial standard due to high output capacity and relative ease in scaling from pilot to commercial scale and maintaining quality aspects of the finished product. However, it remains a costly and complex option and may not be the most ideal option for high concentration suspensions or with limited API supply. Conversely, single- and two-stage cold filling processes are relatively simple to set up and provide an efficient means of preparing pMDIs. Even difficult to deaggregate suspensions can be homogenized as a concentrate with the two-stage cold filling procedure. Yet cold filling is not without its difficulties, as precise temperature control is critical and the product is at increased risk of moisture uptake from condensation or ice formation. To offset these concerns, the two-stage pressure filling process is a suitable alternative. The ambient temperature reduces the risk of moisture absorption while maintaining the ability to prepare the concentrate without pressurization. The two-stage pressure filling process though has a notably lower output rate compared to single-step processes, and accurately dispensing small amounts of concentrate repeatedly is not without complications.

Equally important to the impact on product performance (see Fig. 6) is selecting the manufacturing process that is the most suitable for the drug product. A suspension formulation with high powder load or one that is sensitive, either in size or structure such as a protein, would benefit from a cold filling approach. Conversely, a solution formulation will predominantly be manufactured *via* single-stage pressure filling due to the efficiency gains from speed, ease, and repeatability of that process. As with all formulations, however, there may be exceptions since cost, scale, and familiarity can make a different process more suitable.

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