

Next Generation Formulations for pMDIs

Glyn Taylor, Simon Warren, Cuong H Tran

i2c Pharma Services, Cardiff Medicentre, Heath Park, Cardiff, CF10 4UJ, UK

Summary

Given its 60-year history, it might be tempting to see similarities in physical appearance of the originally marketed pressurised metered dose inhaler (pMDI) with its present form and conclude that little has changed during its lifetime. This however would be specious, since significant advancements have been made in all aspects of the pMDI, including hardware, formulation and performance. The pMDI remains the most widely used inhaler device worldwide for a variety of reasons. Clearly the introduction of the Montreal Protocol with the switch from CFC to ozone-friendly HFA propellants stimulated new research into the fundamental aspects of particle science, device technology and aerosol generation. This has resulted in new strategies to modulate the performance and broaden the applicability of pMDIs. The use of: engineered particles; solubilisation aids including cyclodextrins, and nanoparticles; suspension stabilisers including porous phospholipid particles; lactose and amino acid carrier systems; have all been applied to optimise lung delivery and extend the scope of pMDIs to a wider range of drugs, drug combinations and doses. In addition to small molecule applications, strategies are evolving to formulate macromolecules and biologics, including proteins, DNA, vaccines and bacteriophages. The potential evolution of new propellants with even lower environmental impact will offer future challenges but the wealth of research conducted over the past two decades will help overcome the task ahead. One key driver for the continued development of the pMDI is its global appeal to a broad spectrum of patients.

Introduction

Some key advantages of the pMDIs reside in qualities of being highly popular with patients, robust, compact and portable, highly reliable and quick to use. The pMDI platform is also versatile in many aspects, including the ability to deliver drugs with disparate physicochemical properties in doses ranging from a few micrograms to several milligrams. Clearly there are some disadvantages, and the problem of poor inhaler technique by patients, in particular ineffective co-ordination of inspiration and actuation, is an often cited disadvantage for pMDI use. Other inhaler types, however, also suffer from problems of sub-optimal handling and dosing by patients. The introduction of “smart” pMDIs has been tried in the past but it is hoped that current regulatory ethos and healthcare payment systems will facilitate the widespread use of, devices such as the 3M Intelligent Control Inhaler™ and also that of training aids including Trainhaler™ and Flo-tone™, which are designed to improve pMDI inhaler techniques in patients. A review of these devices is beyond the scope of this article, which will focus on formulation issues.

Despite the environmental success of the Montreal Protocol, the formulation challenges of changing from CFC to HFA propellants with their lower boiling points, different densities, other physicochemical properties and especially the insolubility problems of legacy surfactants, presented significant challenges in re-formulation. The two decades taken post-Montreal Protocol, even in the US, to phase out certain CFC pMDIs, reflects the complexity of replacing certain formulations.

From a positive aspect, the improvements in pMDI performance compared to the CFC formulations have been significant and strategies for enhancements are still progressing. It is perhaps easy to overlook that standard pharmaceutical and medical textbooks, written little more than a decade ago, referred to pMDIs as devices delivering only 5-10% of the emitted dose to the lungs. The performance of modern pMDIs has dramatically increased and they have evolved to be clearly fit for purpose in the 21st Century.

The objective of this article is to review and highlight some of the recent developments in pMDI formulation approaches for both small molecule drugs and also for macromolecules. It attempts to illustrate that the pMDI will remain at the forefront in device choice, offering a viable and highly significant contribution to the management of respiratory diseases and certain systemic therapies.

Discussion

Drugs are formulated as either solutions or suspensions in pMDI products. The challenges of solution formulations are generally those associated with solubility and/or chemical stability of drug in the propellant. In contrast the challenges with suspension formulations are in achieving and maintaining physical and/or physicochemical stability during pMDI manufacture, storage and patient dosing.

Solution pMDI Formulations

Most drugs and biologics are not soluble in HFAs but where a drug has partial solubility, such as beclomethasone, then a co-solvent such as ethanol is needed to ensure that the drug is fully dissolved at the therapeutic doses needed. Other steroids such as ciclesonide and flunisolide are also presented in solution formulations containing ethanol. The amounts of ethanol in the formulation will influence aerosol quality, with high concentrations decreasing the fine particle fraction (FPF)^[1]. Other excipients with low volatility (compared to HFAs) such as glycerol can also be included to modify the aerosol particle size distribution. In addition, pH modifiers are used to maintain chemical stability of some solution pMDIs, such as certain formoterol and ipratropium products. Other excipients include novel functionalized methylated polyethyleneglycols and oligolactic acid, both acting as solubilisation aids when used in combination with ethanol^[1]. The principle of using cyclodextrins as solubilizers in pMDI has also reported, for example with sildenafil (for the treatment of pulmonary arterial hypertension) with FPFs in the range of 45-81%^[2].

Suspension pMDI Formulations

The majority of marketed pMDI products contain drugs formulated as suspensions. Whilst this approach reduces the problem of chemical instability, most micron-sized drug suspensions are inherently physically unstable, to greater or lesser extents, in HFA propellants. Optimizing suspension pMDI formulations to ensure reproducible and effective therapeutic dosing can be achieved using different strategies. One consequence of the Montreal Protocol was the finding that most regulatory approved surfactants at that time were insoluble in HFAs. A number of those surfactants are however soluble to some degree in ethanol, and hence ethanol is a useful excipient in suspension pMDI formulations not only to impart sufficient surfactant solubility, but also functioning alone, as a wetting agent, to aid suspension formation during manufacture and patient use.

Most pMDI suspension formulations contain jet-milled micronised drug particles, however particle engineering technologies including sonication methods, have been developed to generate homogenous particles of well-defined shape and size. In addition, high purity crystals containing different combinations of drugs can be manufactured into a single particle using the "sonocrystallization" technology^[3]. Additionally, this approach does not require additional functional excipients, adjuvants, or co-suspension agents for optimal pMDI performance. A fluticasone pMDI product (Fliveo®, Circassia) employing the sonocrystallization technology has received recent UK and Swedish generic product approvals based upon equivalence data from *in vitro* performance alone.

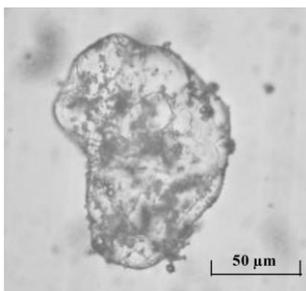
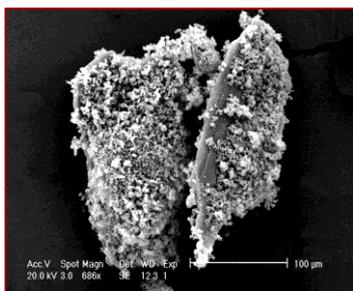
Suspension pMDIs with Particulate Excipients:

Co-Suspension™ Delivery Technology

A different approach to stabilize pMDI suspensions and improve performance is to employ spray-dried porous phospholipid particles, as seen in the Co-Suspension Delivery Technology developed by Pearl Therapeutics/AstraZeneca. The technology uses phospholipid microparticles with aerodynamic diameters of 1–2 µm to irreversibly associate with drug microcrystalline particles during manufacture^[4]. This results to minimize drug-drug interactions and improve suspension stability. Using this strategy, formulations containing either a single drug or combinations of drugs, for example, a corticosteroid, a long-acting beta-agonist and a long-acting muscarinic antagonist, have been developed and can give high aerosol performance with FPFs in excess of 60%^[4]. A glycopyrronium/formoterol product (Bevespi Aerosphere™) using the Co-Suspension technology has recently received FDA approval for use in COPD patients, whilst a glycopyrronium pMDI and a triple combination budesonide/glycopyrronium/formoterol pMDI product are in Phase III of clinical trials.

Opt2Fill™ Technology

The Opt2Fill technology employs a "second particulate" such as micronised lactose, other sugars or amino acids with particle sizes in the range of tens of microns and are readily dispersible in HFAs. The second particulate is first admixed with micronised drug, promoting adsorption of the drug and forming an ordered blend. The second particulate acts as a stabiliser within the HFA environment associating with the drug and minimising aggregation between the high-energy micronised drug particles (Figure1). Upon pMDI actuation and aerosolisation, the micronised drug detaches from the larger second particulate "carrier".



The Opt2Fill technology has applications for both low and high dose drugs such as tiotropium and budesonide, polar and lipophilic drugs such as salbutamol and beclomethasone, and combination formulations including formoterol/budesonide and salmeterol/fluticasone. *In vitro* FPFs in excess of 60% have been reported for several drugs using this type of formulation^[5].

Figure 1 - Opt2Fill Carrier with Adsorbed Drug Particles; (left) after Blending and (right) Suspended in a Model HFA.

In a recent advancement of Opt2Fill pMDI manufacturing methods, the ordered blends of micronised drug and second particulate have been formulated as tablets with the inclusion of a regulatory approved HFA soluble dispersing agent^[6]. The Opt2Fill tablets are then dispensed into cans and crimped. Propellant is then added at a later stage.

In comparison with established pressure fill single- and two-stage manufacturing of suspension pMDIs, the Opt2Fill approach has advantages including the avoidance of homogenization/mixing vessels and pressure vessels, with associated challenges of propellant top-up throughout batch filling. Batch sizes can be readily varied from clinical trial scale to large commercial batches, ensuring process continuity. Additionally, cleaning programmes between different products are greatly simplified. In one example, the in vitro performance of a combination Opt2Fill tablet pMDI formulation of salmeterol xinafoate and fluticasone propionate is shown to be similar to the marketed product^[7] and the effect of formulating the Opt2Fill powder into a tablet is negligible (Figure 2).

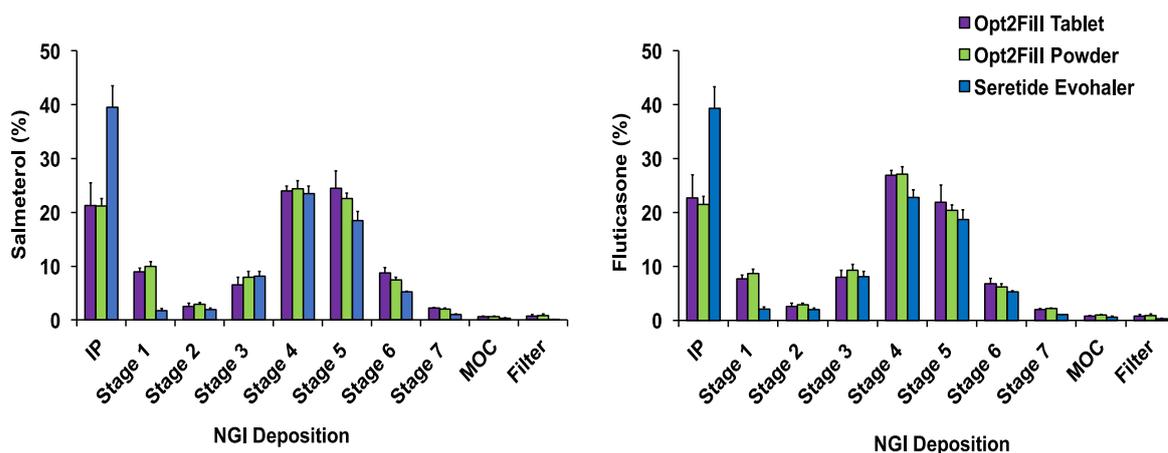


Figure 2 – Aerosol Performance of Salmeterol/Fluticasone pMDI Formulations in the NGI

Macromolecule and Biologic Formulations

The environment within a pMDI formulation is sometimes considered very challenging for macromolecules, especially for proteins to maintain their conformational stability. Despite this, some successes in the formulation of macromolecules have been reported. A very early example is that of crystalline insulin zinc (CFC) pMDI formulations that demonstrated good physicochemical stability over several months, and a predicted shelf-life, with respect to chemical stability, of 19 years^[8]. Clearly many macromolecules and biologics are not readily crystallized and will require sophisticated techniques to maintain their essential structure and potency and produce particles of a suitable size for lung delivery. Studies with nanoparticles of insulin prepared from water-in-oil emulsions formulated into a pMDI with HFA134a and cineole have been reported to maintain primary, secondary and tertiary structures of insulin and gave an extra-fine particle fraction of around 45%^[9]. Successes have also been reported with a number of other macromolecules including DNase, lysozyme, alkaline phosphatase, and bovine serum albumin. Excipients, including vinyl polymers, trehalose and carboxymethylcellulose to either protect the macromolecules during spray-drying, maintain the three-dimensional structure, or to stabilise the suspensions in HFA formulations have been investigated^[10]. Porous (poly (dl-lactide-co-glycolide) microparticles with a density similar to that of HFA227 have also been reported as potential carriers for the delivery of proteins in pMDI formulations^[11].

Research on formulations which may prove suitable for other biologics has also been undertaken. Bains *et al* developed methods using a low-energy microemulsion process to prepare surfactant-coated plasmid DNA (pDNA) nanoparticles. Transfection studies demonstrated that pDNA biological function was preserved following aerosol generation from a HFA134a pMDI formulation. The flocculated system also remained readily dispersible after 5 months and follow-on accelerated stability studies at 40°C/75%RH demonstrated minimal loss of activity over 1 month^[12]. Chitosan nanoparticles have also been used to prepare pDNA in HFA227 formulations and the incorporation into HFA-philic engineered oligolactide core shell particles resulted in FPFs in excess of 50%^[13]. These studies highlight the potential for gene delivery using pMDI formulations. Bacteriophage delivery from pMDIs has also been studied and the potential for delivery of vaccines and phages should not be discounted^[14].

Overall, these studies indicate that the shear forces associated with aerosolisation of macromolecules and biologics from pMDI propellants are not greater, and probably cause less degradation than has been reported previously using air-jet nebulization.

Conclusions

“The pMDI is not dead!” it lives on as an efficient, adaptable and cost-effective method for pulmonary drug delivery. The pMDI is the inhaler device most often used by patients worldwide, and in the UK 70% of inhaler devices sold between 2002 and 2008 were pMDIs. The percentage is however much lower in some other European countries^[15]. Data for recent years (from IMS MIDAS) shows similar trends.

In the 60 years since the introduction of the pMDI, the “mechanical marvel” has faced many challenges, of these the Montreal Protocol might be viewed as its “mid-life crisis”. To accept this however, would be to infer that the pMDI is now in decline and entering the twilight years of its life. Clearly this is not the case and activities in both commercial and academic research are as vibrant now as they have ever been over the past decades.

New propellants may evolve and will present further challenges for the formulators. Given the wealth of knowledge gleaned during the past 25 years we have a much better understanding of the key parameters which influence pMDI performance^[16]. Hence it is inevitable that new strategies will be developed to embrace any future propellant changes and formulators, as previously, will rise to the challenge and seize opportunities for further improvements in pMDI efficiencies.

Clearly the formulation of many macromolecules and biologics will require bespoke solutions but evidence from the radical improvements in pMDI formulations since the CFC-HFA conversion demonstrates that research and innovation in this field will adapt to overcome the inevitable hurdles. This will in part be driven by the inherent advantages of the pMDI for the pulmonary delivery of locally- and systemically-acting drugs.

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