What is the Future of MDIs?

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Introduction

Since their introduction in 1956, the pressurized Metered Dose Inhaler (MDI) has been the most widely used platform used to deliver drugs for the treatment of asthma and COPD. While the basic subsystems of modern HFA MDIs are the same as their early CFC counterparts, each has been substantially improved. Increased regulatory requirements and the transition to hydrofluoroalkane (HFA) propellants have been primary drivers of this innovation (Figure 1). Valves have been improved to function in HFA propellants and meet more stringent regulatory requirements on dosing uniformity and extractables/leachables. Canister technologies (e.g. novel coatings) have been developed to reduce drug degradation and deposition. The transition to HFA formulations resulted in MDIs with increased lung deposition (Figure 2) and technologies to control residual particle size (i.e. the size of the particle remaining after all volatile components evaporate). The transition to HFA propellants led to the development of MDI actuators with improved delivery efficiency. Dose counters have been incorporated for improved patient compliance. Additional improvements are in development. However, it is our opinion that the future of MDIs will be driven more by market factors than by unmet technical requirements. In this paper, we examine factors that will determine the future of MDIs and predict how these factors will shape the next half century of MDI use.

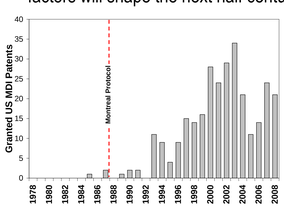


Figure 1. The number of granted US patents with "MDI" in the title, abstract, or claims. Many of the patents granted in the late 1990s were filed shortly after the signing of the Montreal Protocol.

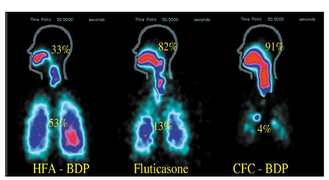


Figure 2. Radioscintigraphy comparison of deposition from HFA beclomethasone dipropionate MDI to two CFC MDIs. (from Leach et al., *Am J Respir Crit Care Med*, 2000, 16(3):A34.

Future of pMDIs – the Authors' Perspective

There will continue to be technical improvements to pMDIs, but the future of pMDIs will be driven more by market dynamics than by technical innovations.

Market Forces Influencing Future of MDIs

The low cost of MDIs (particularly on a cost per dose basis) will be a major factor driving the future of MDIs. Increasing cost pressures in the western countries and the desire for western-style medications in developing countries will secure the future of MDIs. MDIs are particularly well suited for the price sensitive and largely generic developing world markets. We believe that many drug developers will choose to utilize MDIs in order to develop products that will be commercially viable in both developed and emerging markets. We also believe that MDIs will expand into niche markets beyond asthma and COPD.

Key Markets that will Drive Future Sales Growth of MDIs

Developing Country Market Dynamics:

- Desire growing for western style medications
- Cost is critical – predominantly generics
- Millions of untreated asthma & COPD patients
- 300 million asthma sufferers worldwide[1]
- 230 million COPD sufferers worldwide[1]
- COPD growing at 15-20% annually[1]
- COPD expected to be particularly prevalent in developing countries (e.g. as many as 50% of Chinese men smoke[2]). It is estimated that 50% of smokers will develop COPD[3].

Niche Market Opportunities:

- Allergic rhinitis
  - Allows for removal of preservatives
  - Some patients prefer MDIs vs pump sprays
  - Extension of developed MDI formulations (e.g. corticosteroids developed for asthma)
  - Prior to CFC phase-out MDIs were mainstay of AR therapy
- Migraine therapy
- Local delivery of macromolecules for treatment of lung diseases

Political Forces Influencing Future of MDIs

Political dynamics related to the global warming potential of HFC propellants (such as HFA-134a or HFA-227) could influence the future of MDIs. It should be noted that the environmental impact of HFC propellants is much less established than for CFC propellants. While MDIs constituted a small percentage of the total CFC use, CFCs were the overwhelming source from human activity contributing to stratospheric ozone destruction. There is a much weaker link between the HFC propellant use and global warming. HFC propellant is a small contributor of greenhouse gas emissions - approximately 3% of total emissions of CO_2 equivalents in 2007[4]. MDIs constitute a very small percentage of HFC use (<2%). Thus, the contribution of HFA MDIs to global warming is negligible. Despite clear scientific justification for eliminating CFC propellants, CFC MDIs weren't phased out until 21 years after the signing of the Montreal Protocol. There is a far weaker scientific rationale to eliminate HFA MDIs. Additionally, there are ethical factors that must be considered before requesting that developing countries give up access to low cost medications for their citizens. Therefore, it is highly unlikely that HFA MDIs will be forced off the market any time soon, if ever.

Possible Area of Further Innovation: Improved Valves

Fast-Fill / Fast-Empty (FFFE) Designs

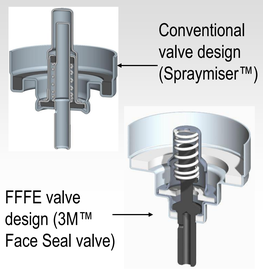
- Benefits: Reduced DTU trending, reduced DCU variability, no priming effects
- Examples: Bespak 'Easifill' valve, 3M™ face seal valve

Coated Valve Components

- Benefit: Reduced DTU trending
- Key challenge: provide durable, complete coating while maintaining dimensional control

Improved Elastomers

- Benefits: Reduced regulatory risk (reduced extractables profile), supply chain control



Possible Area of Further Innovation: Improved Suspension MDIs

One area of continued innovation will be enhancing the stability of suspension formulations. Innovations to achieve this will include: (1) particle engineering of APIs; (2) development of novel excipient technologies; and (3) hardware improvements.

API Particle Engineering Innovations

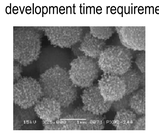
- Potential Goals: Control API crystalization, minimize crystal disruptions, manipulate API particle size and morphology, prevent Ostwald-ripening, etc.
- Example Approaches: SAX™, SCF approaches
- Key Considerations: Must meet cost, scale-up, and development time requirements

Novel Excipient Technologies

- Potential Goals: Minimize settling or creaming, minimize particle agglomeration, prevent Ostwald-ripening, provide sustained drug delivery, enhance chemical stability of API, etc.
- Example Approaches: Pulmospheres®, HFA-soluble excipients, sub-micron bulking excipients, Key Considerations: Must meet cost, toxicology, and development time requirements

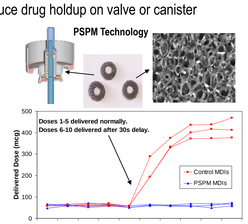
Hardware improvements

- Potential Goals: Improve valve sampling of formulation, reduce drug holdup on valve or canister
- Example Approaches: FFFE valves (e.g. Bespak 'Easifill' or 3M™ face seal valve), new canister coatings, plasma coated valves, particulate semi-permeable matrix[5] (PSPM) for improving sampling, etc.
- Key Considerations: Must meet cost, scale-up, and development time requirements



SAX™ controlled crystalization (www.prosonix.co.uk)

Pulmospheres® (www.nektar.com)



Delivery of Ventolin™ Evohaler™ formulation using Sprayminser™ valves with and without PSPM component.

What Type of Performance Can we Expect from Future MDIs?

- Fine particle fractions > 50%
- Dose-by-dose counting
- Priming-free valves (e.g. FFFE)
- Coated canister and/or coated valves
- 'Tunable' particle size distributions
- Particle engineering for suspension formulations
- Bulking excipients for solution formulations
- Breathe-actuation?

What Remains to be Done?

Technical Solutions Yet to be Developed:

- 'Universal' valve (e.g. formulation independent)
- Formulation approach to make more drugs into solution formulations

Technical Solutions Developed but Yet to Gain Widespread Market Acceptance:

- Breathe Actuation
- FFFE valves
- Low number of doses (e.g. 30 or less) pMDIs
- Proteins and peptides MDI formulations
- Particle engineering technologies for improved stability or delivery
- Improved efficiency actuators / integrated spacers

Conclusions

There have been significant improvements in virtually every aspect of MDI technology since the first MDI was developed in 1956. On the other hand, modern HFA MDIs bear many similarities to earlier designs. We anticipate that in the future there will be numerous enhancements to MDIs, but that the MDI 50 years from now will not look drastically different from current MDIs. Growth in the MDI market will be driven by the demand for low cost inhalers in the western world and even more so in developing countries. We do not anticipate that regulatory actions associated with global warming will lead to a ban on HFA MDIs.

References:

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