INTRODUCTION

The Human Respiratory System

The human respiratory tract can be divided into 24 generations. Regarding physiological functions, the contiguous airway from the trachea to the terminal bronchioles is called the conducting zone, and the areas from the respiratory bronchioles to the alveolar sacs (generation index 17–23) are called the transitional and respiratory zone.

Asthma & Chronic Obstructive Pulmonary Disease (COPD)

Respiratory diseases like asthma and Chronic Obstructive Pulmonary Disease (COPD) are a common cause of morbidity and mortality worldwide.

In Nepal, a combination of asthma and bronchitis constitutes a major cause of mortality. Bronchodilators and anti-inflammatory agents are important for the treatment of these diseases.

On systemic administration, these agents produce considerable side effects. In order to overcome this problem and to have a quicker onset of action and better efficacy, inhaled medications are preferred. However failure of treatment is still a common problem for these diseases. One of the reasons for this is incorrect use of Metered Dose Inhalers (MDIs), the commonest method of inhaled drug delivery. It has been demonstrated to occur approximately in 75% of the patients using MDIs.4

FORMULATIONS4

In general, MDI formulations can take the form of either suspensions or solutions. Traditionally the preferred route has been to formulate a suspension of the micronized drug substance in the liquid propellant (CFC or HFA). In some cases, additional excipients (e.g., surfactants and/or cosolvents) have been added to improve the quality of the dispersion. Quality control testing of MDI batches is applied to the individual inhaler components prior to manufacture, as in-process controls during the manufacturing, and to the finished product. An exhaustive search for new propellants was made at the time of the switch away from CFCs, and it is unlikely that new ones will be found with the necessary physicochemical properties combined with an excellent safety profile.

KEY WORDS - Metered dose inhalers, Solution, Suspension

ABSTRACT

The MDI is now established as the principal dosage form of inhalation drug therapy for bronchial asthma and chronic obstructive pulmonary disease (COPD). Metered dose inhalers (MDIs) are pharmaceutical delivery systems designed for oral or nasal use, which deliver discrete doses of aerosolized medicament to the respiratory tract. The MDI contains the active substance, dissolved or suspended in a liquefied propellant system held in a pressurized container that is sealed with a metering valve. In general, MDI formulations can take the form of either suspensions or solutions. Traditionally the preferred route has been to formulate a suspension of the micronized drug substance in the liquid propellant (CFC or HFA). In some cases, additional excipients (e.g., surfactants and/or cosolvents) have been added to improve the quality of the dispersion. Quality control testing of MDI batches is applied to the individual inhaler components prior to manufacture, as in-process controls during the manufacturing, and to the finished product. An exhaustive search for new propellants was made at the time of the switch away from CFCs, and it is unlikely that new ones will be found with the necessary physicochemical properties combined with an excellent safety profile.

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TYPES

A. Non-pressurised metered dose inhaler: portable, inhalation delivery device containing an aqueous solution, suspension or emulsion, which delivers one dose in one (or more) actuation(s).

B. Pressurised metered dose inhaler: an inhalation product containing one or more propellants in a pressurised delivery device.5

Pharmaceutical Development Studies for Inhalation Products5

- Drug delivery rate and total drug delivered
- Shaking requirements (For suspensions.)
- Initial & repriming requirements
- Cleaning requirements
- Low temperature performance
- Performance after temperature cycling
- Effect of environmental moisture
- Robustness
- Delivery device development
- Preservative effectiveness/efficacy (If a preservative is present.)
- Compatibility
FORMULATION CHEMISTRY

Interactions of the basic MDI formulation components:

- Drug active
- Surfactant
- Co-solvent
- Propellant

In doing so, each formulation component was characterized by certain physical properties judged to be important to the surface interactions.

The MDI medicaments were characterized by:

- Log p value (Octanol-Water partition coefficient)
- Density
- Particle size
- Surface energy
- Morphology

The propellants were characterized by:

- Density
- dielectric constant

The surfactants were characterized by:

- head/tail structure
- molecular weight
- chemistry

Table 1: Important formulation patents

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Patent</th>
<th>Company</th>
<th>Priority date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol/HFA-134a EP 0372777</td>
<td>3M Health care</td>
<td>Priority date 06/12/88</td>
<td></td>
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<tr>
<td>HFA-227 and mixtures EP 513099</td>
<td>Boehler Ingelheim</td>
<td>Priority date 03/02/90</td>
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<tr>
<td>HFA Propellant only WO 93/11744</td>
<td>Glaxo priority date 12/12/91</td>
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<tr>
<td>PVP/PEG/HFA WO 93/05765</td>
<td>Fisons (Aventis) priority date 25/9/91</td>
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PROPELLANTS

The propellant or propellant mixture used in the MDI provides the energy necessary to generate a fine aerosol of drug particles suitable for delivery to the lungs or nasal cavity. Liquefied compressed gases are preferred over non-liquefied compressed gases such as nitrogen or carbon dioxide because they offer the following critical advantages for inhalation therapy:

- The discharge of defined aliquots of propellant from the MDI will undergo flash evaporation to give an aerosol of very small particles.

- The pressure inside the MDI remains constant throughout the use of the entire contents, thus ensuring that the aerosol characteristics remain uniform during repeated discharges. At constant temperature, the vapor pressure remains constant while liquefied propellant remains. In contrast, aerosols generated using non-liquefied compressed gas coarsen during emptying of the MDI due to the decrease in gas pressure. However, unlike non-liquefied compressed gases, the vapor pressure of liquefied propellants decreases significantly with decreases in temperature, such that below a certain temperature, the flash evaporation process is sufficiently retarded to give poor aerosol formation.
The ideal propellant for use in an MDI will exhibit the following properties:

- Non-toxic
- Inert and non reactive in the formulation
- Chemically stable under a range of conditions
- High purity
- Acceptable taste and odor properties of metered dose inhalers:
  - Compatible with the packaging components (can, valve, actuator)
  - Suitable vapor pressure
  - Suitable density to facilitate suspension stability
  - Suitable solvency properties
  - Preferably non-flammable
- Acceptable cost

**HFA MDI solution formulations**

In an HFA MDI solution formulation, the drug is completely dissolved using an HFA propellant (e.g., 134a) plus an appropriate co-solvent to produce a pure solution product. The co-solvent most commonly used is ethanol. This approach has been used successfully to produce a solution aerosol product for BDP. There are a number of advantages to a formulation of this type:

1. Potentially fewer issues around homogeneous valve sampling from the bulk.
2. As in the case of the BDP solution aerosol, enhanced efficiency of aerosolization, leading to high lung deposition compared with an equivalent suspension product.
3. Overcomes issues with suspension systems where the drug has measurable solubility in the propellant, i.e., formulation does not suffer from particle growth issues.
4. There is always sufficient co-solvent present to preserve the true solution status of the product, no issues with drug deposition on the valve components and container.
5. May be a simpler filling process than for a suspension-based HF MDI.

There are also a number of disadvantages to true solution MDI products:

1. Solution products can be more susceptible to drug losses into the elastomeric components of the valve than for an equivalent suspension product. Drug losses of this kind can be an issue particularly for low dose products.
2. There are currently few options beyond ethanol in terms of co-solvents that would be Generally Regarded As Safe (GRAS). Thus, to develop a solution formulation using a co-solvent other than ethanol could necessitate an extensive toxicology testing program. Of the currently available respiratory drugs, there are few that are sufficiently soluble in ethanol or sufficiently low in strength to easily yield a solution product.
3. If too much ethanol is used to dissolve the drug, the vapor pressure may drop below that required to achieve efficient atomization.
4. If the product under development is transitioning from an existing CFC suspension-based product, it may be difficult to replicate the fine particle mass, the particle size distribution and/or the absorption characteristics. This can lead to problems in providing a seamless transition from the CFC product because of the potential to have to change the dose and because the product can smell and feel different to the original suspension formulation.

More recently, other (less volatile) organic modifiers, e.g., glycerol, have been added to solution-based HFA MDIs to modify the particle size distribution so that it more closely resembles that of the originator suspension product.

**HFA MDI suspension formulations**

There are a number of possible approaches to a suspension-based formulation. A micronized drug can simply be suspended in an HFA propellant or a mixture of HFA propellants. The principal advantage to a formulation of this type is that it is simple and contains no additional excipients with their inherent toxicological implications. The performance of a formulation of this simplicity will be dependent on the inherent properties of the drug substance and the propellants used. For example, if the drug substance is significantly more dense than the propellant(s) is, then rapid sedimentation of the suspension is likely to occur following agitation. This could create issues in terms of the valve sampling homogeneously from the bulk container contents. Further differences between the drug and propellant in terms of relative hydrophobics and hydrophilics can also result in rapid flocculation immediately post shaking or a tendency for the drug to deposit on the MDI container walls and valve components. For the approach of creating a dispersion of drug in propellant to be successful, the drug should essentially be insoluble in them propellant(s) to provide good product stability.

**CONTAINERS**

The essential requirements of containers used for MDIs are that they are compatible with the formulation, have an ability to withstand internal pressures up to 1500 kPa, and can be manufactured with reproducible quality. The most widely used containers for MDIs are made from an aluminum alloy, although glass bottles have also been used. Aluminum containers (cans) are preferred due to their light weight, strength, break resistance, compactness, and ability to provide light protection.

Glass bottles are not widely used because of their greater weight and potential fragility. Glass containers used with pressurized liquefied propellants are externally coated with a plasticized polyvinyl chloride (PVC) layer to retain glass fragments in the event of breakage.

The optimum crimp parameters will permit correct valve function and minimize propellant leakage.

**Valve:** Component Function Gasket Seal between the valves and can; usually made of rubber.

**Ferrule:** An aluminum cup that holds the valve components together and attaches them to the can in the crimping process.

**Stem:** Moving part of the valve that provides the metering action and connects the valve to the actuator. Its design provides entry and exit ports to the metering chamber to permit filling and discharge of the metered dose respectively.

**Seat:** Provides the main seal around the valve stem and is usually made from rubber. Most valves have two seats to provide the metering action.

**Spring:** Returns and holds the stem of the valve in the rest position after actuation, located inside or outside of the metering chamber.

**Metering chamber:** Defines the volumes of liquid discharged. Valves with 25-, 50-, 63-, and 100-ml nominal metering volumes are available.
ACTUATORS AND SPACERS
Overview of the Components for the Basic MDI Actuator For a simple MDI, the actuator is a one-piece plastic molding that performs a number of critical functions as a key packaging component in the overall system. The main plastic body of the actuator surrounds and protects the aerosol canister, and veins within the actuator help to locate the canister so that when it is depressed by the patient to release the dose, the canister moves straight down without flexing the valve stem. A high degree of flex could result in poor performance, e.g., as a result of continuous spraying of the valve. The veins also serve to centrally locate the canister within the actuator body to create airflow paths with minimum resistance so that air can be easily drawn through the device as the patient inhales. The actuator also incorporates the stem block containing the spray nozzle. The stem block contains a socket that the valve stem pushes into when the canister is placed inside the actuator.

BREATH OPERATED INHALERS AND OTHER DEVICE ENHANCEMENTS
The MDI has proved itself over many years of successful use as a highly effective method for delivering drug to the lungs for the treatment of respiratory disease. The MDI is simple to use for most people, but there are difficulties that certain sectors of the patient population may have with the use of this device type. Patients who have this coordination difficulty can either be supplied with a dry powder inhaler (where the inspiration through the device is also responsible for the release and aerosolization of the powdered drug so that coordination is no longer an issue), or they may be prescribed a Breath Operated Inhaler (BOI) 14.

Breath Operated Inhaler (BOI).
Several of these device types are marketed; they are still MDIs but the device takes over the responsibility for actuating the can as the patient breathes in. Typically, the device is primed immediately before the patient takes their dose. This priming can be achieved either via the opening of the dust cap to reveal the mouthpiece or by operating a special priming lever. For the currently marketed devices, this results in a spring being compressed above the aerosol canister that has enough strength to actuate the canister release.

Some breath-actuated inhalers are described below, and several others are currently in development.

Autohaler
An early model of the Autohaler breath-actuated device was described over 30 years ago,41 but it operated noisily and some patients could not generate the necessary flow to trigger the device. The current Autohaler device (3M Pharmaceuticals, St Paul, Minnesota) overcomes these limitations, since it is quiet and can be triggered by a flow of only 30 L/min.

Easibreathe:
The Easibreathe is a pMDI actuator, originally developed by Norton Healthcare (London, United Kingdom). In some ways it resembles the Autohaler, but is simpler to use because opening the mouthpiece automatically prepares the device for inhalation. The Easy breathe contains a pneumatic system, which restricts the operating spring. Actuation occurs in synchrony with inhalation at only 20L/min.

K-Haler:
With the K-Haler breath-actuated device (Clinical Designs, Aldsworth, United Kingdom), the dose is actuated into a kinked tube, which is straightened by a breath operated lever, which releases the dose.

MD Turbo:
The MD Turbo (Respirics, Raleigh, North Carolina) is a breath-actuated inhaler that can accommodate various pMDI products. It incorporates “i-Point” technology, with which actuation only occurs at a pre-determined inspiratory flow.

Xcelovent:
Another breath-actuated pMDI device, the Xcelovent, designed by Meridica (Melbourne, United Kingdom), delivers an HFA formulation containing budesonide and formoterol. Xcelovent may in the future be developed by Pfizer (Sandwich, United Kingdom).

Other Novel Devices
Breath-actuated inhalers and breath-coordinated inhalers do not attempt to solve the cold-Freon effect problem, 37 but devices with slower spray velocity are likely to help. At least one device is already marketed, and several others are in development. In 1989, Byron et al46 reported that it is possible to reduce the non respirable fraction by placing baffles near the actuator nozzle, to intercept large, rapidly moving droplets. However, no devices based on this principle seem to be in development.

Spacehaler:
The Spacehaler (Celltech Medeva, Slough, United Kingdom), formerly known as the Gentlehaler (Schering- Plough, Kenilworth, New Jersey), is a compact, low-velocity spray pMDI, 7.5 cm in length. The device produces a rapidly spinning vortex at the actuator nozzle, which reduces the initial spray velocity to approximately 2 m/s, which decreases oropharyngeal deposition and probably provides better lung deposition than a standard pMDI.

Spacer Design
Spacer devices are also known as add-on devices, accessory devices, extension devices, and holding chambers. They are attachments to pMDI actuators, with volumes ranging from 20 mL to 750 mL in commercially available models. Spacers perform several functions. By placing some distance (and, thus, time) between the point of aerosol generation and the patient’s mouth, they reduce oropharyngeal deposition and increase lung deposition 14.

QUALITY CONTROL
Quality control testing of MDI batches is applied to the individual inhaler components prior to manufacture, as in-process controls during the manufacturing, and to the finished product.

Quality control and analytical tests1:
Individual component testing
• Containers
• Metering valve
• Mean weight per actuation and leakage rate
• Input micronized drug
• Propellant
• Surfactant
• Actuator

In process control testing
• Atmosphere condition
• Drug suspension concentration
• Drug suspension
• Filled canisters
• Gross leakage and safety
Analytical testing applied to finished product

- Control of leakage rate
- Metering valve function

Drug Product Specification Tests for Inhalation Products

- Description
- Assay
- Identity
- Microbial limit test
- Spray pattern
- Water content
- Foreign particulate matter

(a) Description
A description of both the formulation and the full delivery device (e.g., including actuator) should be given where applicable. For products for nebulisation, the immediate packaging should be described (e.g., translucent LDPE nebulae).

(b) Assay
For multi-dose products, the amount of drug substance should be determined per weight unit or per volume unit, as applicable. For single dose products, the assay should be expressed as mass per dosage unit. The usual assay limits for medicinal products apply.

(c) Moisture Content
The limit for moisture content should be established based on results seen in stability studies. If the results are stable throughout the shelf life of the product, or if any changes in moisture content do not result in changes to any other parameters, it may be acceptable to omit this test from the specification; this should be fully explained in the Justification of Specification(s) section.

(d) Mean Delivered Dose
The amount of drug substance in one actuation should also be determined by calculating the mean of the delivered dose uniformity test results, with corrections as necessary to convert from “per dose” amounts to “per actuation” amounts. Limits of ± 15% of the label claim apply.

(e) Delivered Dose Uniformity
The delivered dose uniformity test should be conducted according to an accepted pharmacopoeial method, or a suitably validated alternative. Limits applied should be consistent with the pharmacopoeia, with adaption as necessary to test both intra- and inter-device variability. The use of uniformity of weight per actuation in lieu of content uniformity may be acceptable for solution formulations. Justification should be provided. Content uniformity should be investigated on samples removed from the containers as per the instructions provided to consumers and health care professionals. Acceptance limits should be justified, taking into consideration pharmacopoeial requirements. The use of

(g) Fine Particle Mass
The fine particle mass test should be conducted using a validated multistage impactor or impinger method, or a suitably validated alternative. It is normally considered acceptable to set upper and lower limits on the results of pooled stages corresponding to a particle size distribution of less than 5 m, although alternative limits may be found acceptable with adequate justification. The drug mass should be reported rather than the percentage of emitted dose (or other derived parameter). Additional criteria may be appropriate such as grouped stages or limits for mass median aerodynamic diameter (MMAD) and / or geometric standard deviation (GSD) if the fine particle mass alone is insufficient to fully characterize the particle size distribution of the therapeutic dose. Control of the particle size distribution above 5 m may be necessary depending on the relevance of this fraction for the therapeutic index of the product. In all cases, limits should be qualified by the fine particle mass results for batches used in in- vito (pivotal clinical and/or comparative) studies and should be reported on a per actuation or per dose basis.

(h) Leak Rate
A leak rate test and limits should be included in the specification.

(i) Microbial / Microbiological Limits
Microbiological quality testing should be conducted according to an accepted pharmacopoeia test, or justification for not including this test should be included in the Justification of Specification(s) section.

(j) Sterility
Sterility testing should be conducted according to an accepted pharmacopoeia test.

(k) Leachable
Depending on the results of the pharmaceutical development study on extractables and leachable, and in particular the results of safety, a test and qualified limits for leachable should be included in the specification.

(l) Preservative content
Preservative assay testing should be conducted.

(m) Number of actuations per container
The number of actuations per container should be demonstrated to be no less than the labeled number of actuations.

Disadvantages for MDI aerosol evaluation:
- Drug containing particles are not distinguished from excipient or foreign particles.
- Aerosol sampling may not be representative due to inadequate measurement of the large particles and their possible partial loss in the sampling probe.

Patient Education
Patient training is important for the proper use of aerosol devices. In a recent study, data were collected concerning treatment regimens, the ability of parents to use a device, and the acceptance of the devices. Even though physicians were aware of the purpose of the study, no explanation or training in administering the treatment was given to 47% of the parents by the prescribing pediatrician. Errors in using the devices and in administering therapy were much more common when training was not offered.
CONCLUSION
Metered dose inhalers (MDIs) are the most popular vehicle for drug delivery into the lungs and some 500 million are manufactured each year. Metered-dose inhalers are only one type of inhaler, but they are the most commonly used type. The replacement of chlorofluorocarbons propellants with hydro HFA resulted in the redesign of metered-dose inhalers in the 1990. The proper use of the MDI is crucial for the delivery of many asthma medications. The results of this study suggest that children as well as every individual need intensive education before they can learn and remember how to use their MDI correctly.

FUTURE SCOPE
An exhaustive search for new propellants was made at the time of the switch away from CFCs, and it is unlikely that new ones will be found with the necessary physicochemical properties combined with an excellent safety profile. However if possibilities do emerge they should be evaluated. New surfactants are possible, but there is the major cost hurdle of drug toxicity studies to NCE standards. Particle engineering may provide benefits, for example, production by supercritical fluid technology or hollow particles. Devices are starting to appear, which contain electronics and batteries, and this allows the possibilities for extensive feedback to both patient and physician.20

ACKNOWLEDGMENT
I am very thankful to Principal of Modern College of Pharmacy (For Ladies), Moshi, Pune and S.N.D. College of Pharmacy, Babhulgaon, Yeola, Nashik for supporting me each and every step of my work.

REFERENCES