Inhalation Technology

A breath of fresh air in drug delivery!

Dr. Thilo Schmierer,
Business Development Manager

Corinne Malica,
Pharmaceutical Market Specialist

Introduction

The inhalation route is a fast and effective way of delivering medication locally to the lungs and also for the systemic administration of certain agents. Inhalation drug therapy is used extensively to treat respiratory conditions such as asthma and Chronic Obstructive Pulmonary Disease (COPD). Recently, it has been shown that pulmonary drug delivery could also be an effective route to deliver drugs to the systemic circulation thanks to the large surface area of the lungs with highly vascularised epithelia.[1] Research is ongoing to develop inhalation systems to treat neurological disorders, cystic fibrosis, pain management and to deliver vaccines.

The Metered Dose Inhaler (MDI) is the original and most widely used device to deliver inhalation therapies. It uses pressurized gas to release its dose when activated by the patient. More recently, the Dry Powder Inhaler (DPI) has been gaining popularity because it does not rely on propellant to deliver the medication and patients find it convenient and easy to use.[2] Other systems available on the market include liquid droplet inhalers and nebulisers. When developing a new product, researchers can select either a standard inhaler device or decide to develop a customized solution that is more tailored to the requirements of their product and the particular disease area.

Whatever solution is chosen by the company, the effectiveness of the technology will also depend on the ease of use and the patient's ability to administer his or her own medication. It is therefore essential that the device is designed using a patient-centered approach. Generally, patients express preference for devices that are small, portable and easy to use whilst always ensuring that an accurate dose is dispensed. From the company's point of view, the selected device must meet stringent manufacturing requirements in terms of its robustness, efficiency and precision whilst remaining environmentally friendly.

Inhalers –
opening up the airways in respiratory disease

The burden of chronic respiratory diseases such as asthma and COPD on patients is significant in both physical and psychological ways. Narrowing of the airways causes breathlessness which, during an acute attack, can lead to asphyxia and death if medication is not administered rapidly. Even normal physical activity can be exhausting, whilst smoke, allergens, or even expressions of emotion such as laughter or crying can trigger an asthmatic attack or cause an exacerbation of COPD. Fear of provoking an acute attack makes patients anxious, forcing them to limit their daily activities and making them completely reliant on their inhalation product.

> *"COPD is extremely disabling for me. It's exhausting not being able to climb stairs without pausing between each floor."*
> ***Female COPD patient***

> *"Asthma is a disease still considered as "easy to manage". You just need to have the proper medication. However, living with it is a constant handicap for all activities."*
> ***Male asthma patient***

PRIMARY	
Easy to use	• To avoid additional stress during an acute attack • Simple treatment implies a less "serious" disease that is under control
Discreet	• The device should not attract attention during administration • Small – it should fit into the palm of the hand • Unobtrusive style without bright colours to avoid appealing to children
Portable	• Should fit easily into a trouser or jacket pocket
Visible dosing	• Remaining doses should be visible to allow the patient to anticipate when a new prescription will be required
SECONDARY	
Easy dose loading	• Should be possible to load dose into the device quickly and hygienically
Clean and hygienic	• Should be simple to protect and clean the mouthpiece
Separate device and doses	• To avoid additional costs and wastage

Figure 1: Key physical attributes for an inhaler delivery system

Generally, chronic respiratory patients are knowledgeable about their disease and its treatment; they become experts in juggling between different inhaler devices for everyday use or crisis management and in adapting their lifestyles, as well as their medications, to meet the demands of their illness. Nevertheless, patients often feel embarrassed about appearing "sick" and being stigmatized in the outside world where such diseases are poorly understood.[2] This means that inhaler systems used to treat respiratory disease should not only be effective in delivering precise doses, they should also be small, discreet, easy to carry and easy to use.

Recent market research highlighted various practical aspects mentioned by patients familiar with inhaler use.[2] The men and women interviewed were between 20 and 60 years old and were suffering from COPD or chronic asthma. They had all been using inhalers on a regular basis for at least a year and had experienced at least two different systems (blister, capsule or aerosol). When questioned, the patients defined key design criteria for inhalers as straightforward dose loading, being able to clean and protect the mouthpiece, and that the device and the dose should be available separately to avoid wastage *(Figure 1).*

> *"A 'good' inhalation system for me is a system that is efficient (fast action) and easy to use, because when a crisis occurs a state of 'panic' can set in, and so there should be no additional stress with a system that is complicated, and finally it should be correctly dosed and well adapted to the degree of asthma and the patient's pathology"*
> ***Respiratory Clinician***

During the same study, experienced patients were asked to assess the relative merits of the main inhalation systems currently available: sprays, blisters and capsules. Sprays have been on the market for a long time and the metered dose inhaler (MDI) is the reference inhaler device. MDIs are prescribed mainly for emergency use whilst dry powder inhalers (blisters or capsules) tend to be preferred for everyday maintenance therapy *(Figure 2).*[2]

Although sprays are small and simple to use, they do have some drawbacks: for instance there is no indicator for the number of remaining doses in the device so that in a life-threatening situation, like an acute asthma attack, the patient cannot check whether sufficient doses have been delivered. As sprays can discharge accidentally, the lack of dose counting is even more worrying. Also the mouthpiece tends to get dusty and requires scrupulous cleaning. Finally, patients using MDIs need to carefully regulate their breathing to ensure that the full dose is inhaled.

Blister based inhalation devices are perceived as a more modern approach. These devices are easy to load and to clean. However, their design is bigger and bulkier than other inhalers and the devices are more conspicuous when used in public.

Patients involved in the market research considered capsule-based systems to be very effective in ensuring precise dose measurement.[2] There is less wastage compared to blisters because the capsules and the device are available separately and the capsules are biodegradable and hence environmental friendly. Loading is considered to be straightforward by the

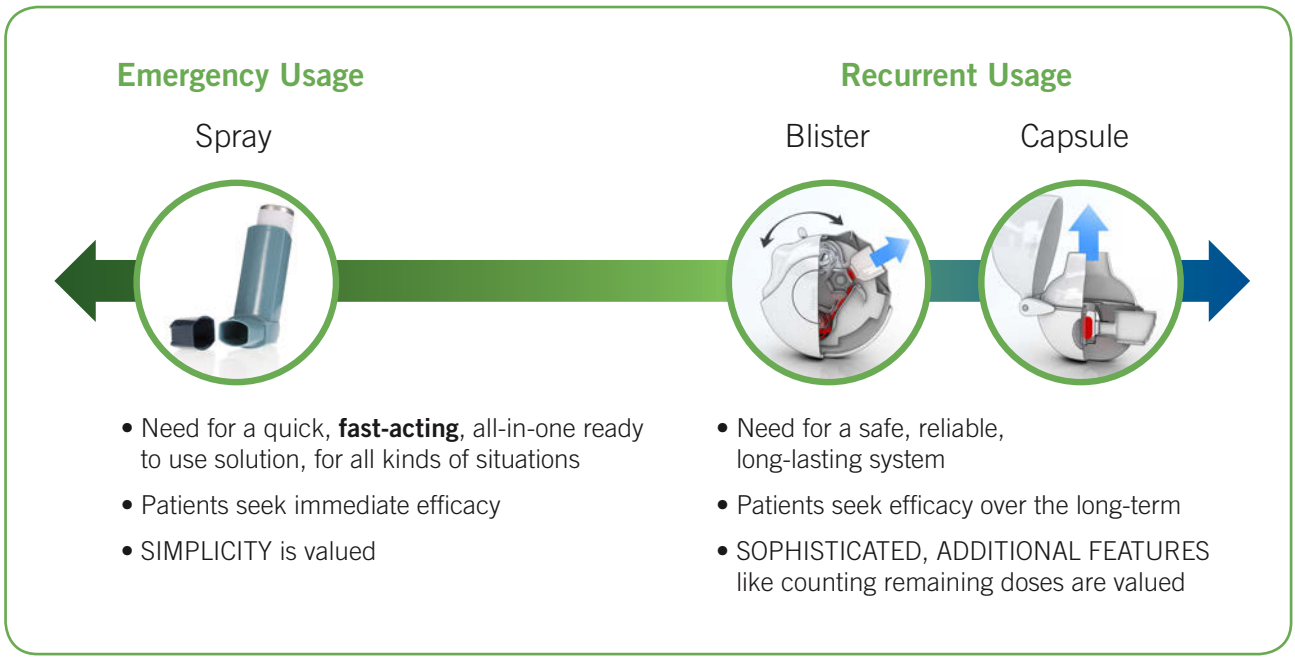

Figure 2: Comparison of inhalation systems: Patient perception influenced by device usage

majority of patients although for some non-users there is a perception that capsules could be more complicated.

Although MDIs are the market leader with 48% of retail sales in Europe versus 39% for DPIs and only 13% for nebulisers[3], they are gradually losing their popularity to be replaced by technically superior and more eco-friendly DPIs.

Dry Powder Inhalers – not only for respiratory disease

The progress of DPI technology has created opportunities in other therapeutic areas where systemic exposure is required. Low dosed drugs and large molecules have been successfully delivered via the respiratory tract for the treatment of systemic diseases. Potential indications include pulmonary arterial hypertension, neurological disorders such as Parkinson's, hereditary diseases, and pain management including migraines and vaccines.

Inhaled drug therapy is an appealing option for patients because of its painless and flexible administration compared to injections. Compared to oral administration, it has the advantage of a more rapid onset of action, lower dosing, avoidance of first pass metabolism and potentially fewer side-effects *(Figure 3).*[1]

- Less drug could be required compared to oral administration
- Onset of action can be more rapid via inhalation compared to the oral route
- Adverse effects are potentially less severe and less frequent
- Drugs that are not absorbed orally can be delivered via the lung
- Compared to injectable dosage forms, inhaled drug therapy is painless and relatively comfortable for the patient which encourages compliance

Figure 3: Advantages of inhaled drug delivery for treating systemic disease

One area of interest for DPIs is in inhaled antibiotics for the unmet medical need of treating cystic fibrosis, a life threatening lung disease and several studies are ongoing in this indication[4]. In 2010, Novartis gained EU approval for a dry powder inhaler for tobramycin (TOBI® Podhaler®)[5] and the FDA granted Orphan Drug Designation for a ciprofloxacin DPI[6].

Another indication for the use of DPIs is for the treatment of viral infections. Zanamivir® (Relenza®) from GSK is a neuraminidase inhibitor that is used for the treatment and prevention of influenza. It is formulated as a dry powder and packaged in four 5mg blisters on a Rotadisk® for inhalation via the Diskhaler®.

In February 2010, Daiichi Sankyo filed a New Drug Application in Japan for its influenza drug CS-8958, which is delivered using Hovione's TwinCaps® inhaler. Applications are expected soon via Hovione's licensee Biota for Europe and the US markets.

Proprietary DPI technology – how to stand out from the crowd

To take advantage of opportunities for inhalation drug delivery in both respiratory and systemic diseases, manufacturers of inhalation drug therapy are focusing on the development of proprietary technology platforms for efficient development and manufacturing as well as to differentiate themselves from the competition.

Strategic decisions are primarily based on:

- Cost efficiency
- Patient acceptability
- Development timelines
- Patent protection of the proprietary solution

> *"We use a capsule-based system. We were granted a patent for a combination using HPMC capsules and a capsule-based DPI device"*
> ***R&D director, Pharmaceutical Company***

The choice of the system can be made at a very early stage before product development has begun. Input is usually sought from business development and marketing specialists to ensure that the proposed system is in line with market trends and will meet customer needs. In early development stages, R&D works closely with management to look at product performance, feasibility and timing in addition to the cost of goods and the position of the new product within the company's pipeline and product portfolio. As the project moves ahead studies are required for formulation development, compatibility and stability, feasibility and scaling up as well as for the clinical programme.

The overall approach to the choice of technology and the device will depend on the company's business strategy. A big pharmaceutical, R&D based company will prefer to develop or use its own existing proprietary technologies and will work on formulating the Active Pharmaceutical Ingredient (API) to fit the inhalation drug delivery system. Smaller companies, if not specialized in inhalation drug therapy, will usually seek outside help from device manufacturers to find the

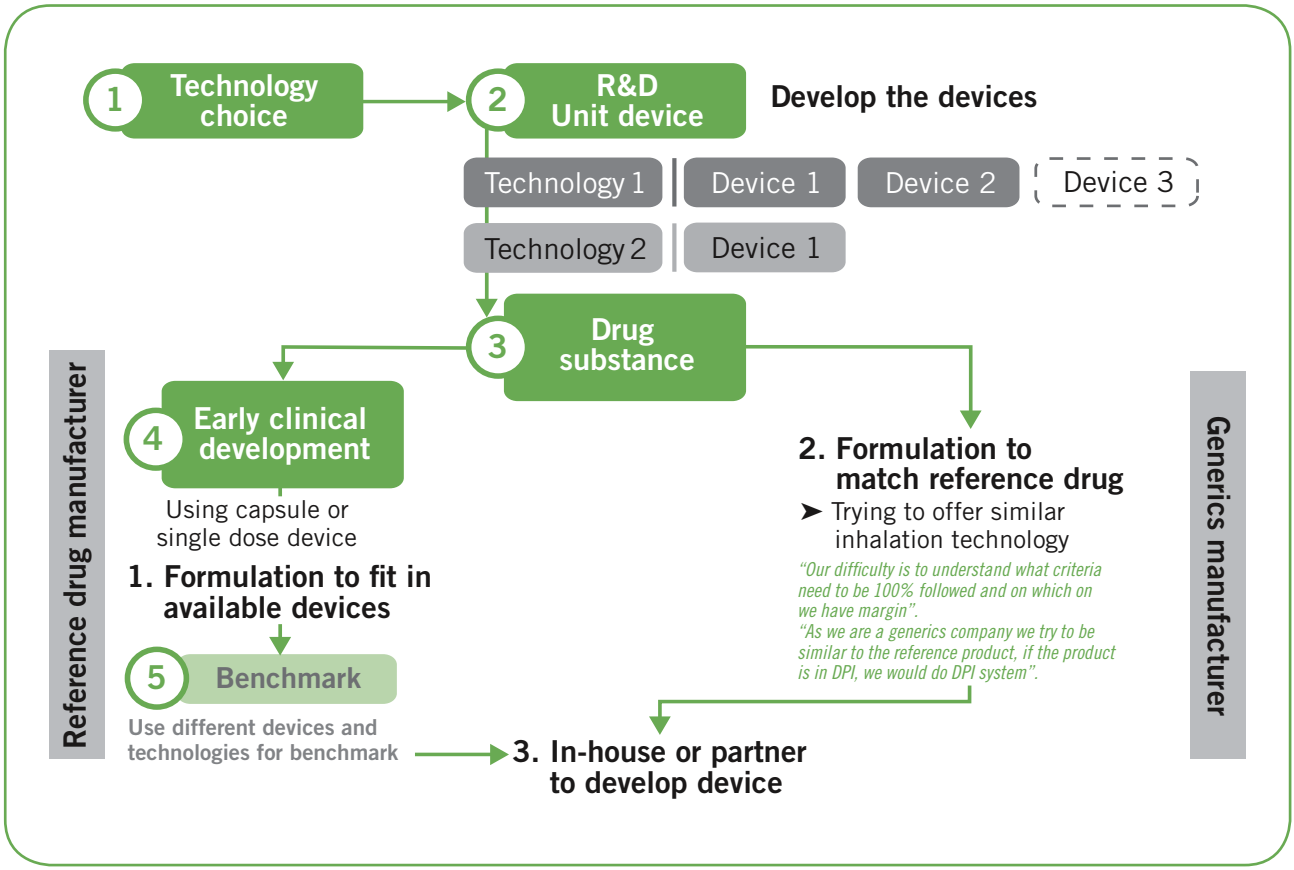

Figure 4: Development processes for inhalation systems

best available system for their drug *(Figure 4)*.

The considerations that influence the manufacturer's decision process when developing a DPI include dosing, performance, cost efficiency, device size, number of doses, and functionalities that can offer added value and product differentiation in terms of patient acceptability e.g. simple to use, eco-friendly, hygienic and portable *(Figure 5)*.

The most popular DPI technologies are either blister or capsule based.[7] Both delivery systems offer comparable performance in high accuracy dosing. However, blisters rely on more cumbersome, high precision devices for their administration. The blister devices tend not to be so popular with patients and seem to be more expensive to produce compared to capsule systems.[2,7] The advantage of blister based systems may be their suitability for highly moisture-sensitive products.

When the decision has been made to opt for a capsule-based system, a capsule supplier is the ideal development partner. A recent market survey found that Capsugel, the market leader in two piece capsules, was the first supplier mentioned by respondents.[7] Researchers noted that existing customers particularly appreciate the development and manufacturing support provided by Capsugel throughout the development and commercialization process that ranges from

> *"...consultation to services for development and manufacturing"* ***R&D, Pharma company***

The choice of the capsule and capsule supplier is as important as the selection of the inhalation device in terms of the technological suitability, patient needs, product performance and possibilities for product differentiation (e.g. device design, capsules branding). Customisation of capsule-based inhalation systems remains the most effective way of adding value and making the product stand out from its competitors.

CRITERIA	LIMITING FACTORS
Dosing • Accurate • Consistent **Performance** • Enhance administration of drug • Lowest resistance to airflow • High lung deposition **Functionalities → bring added value and differentiation for patients** • Convenience of usage • Number of manipulations • Ease of loading the device • Number of doses to be delivered • Compliance of patient	**Cost** • Cost per dose **Performance** • Moisture • Protection of dose **Size of device depending on number of doses**

Figure 5: Criteria for the development of an inhaled delivery system

Conclusions

Inhalation technology is used extensively for the local treatment of chronic respiratory diseases such as asthma and COPD and also in other indications such as influenza or pain management that require a rapid onset of action and can be treated systemically via the lungs.

The global market for pulmonary drug delivery is growing rapidly and is expected to reach US $37.7 billion within the next five years with the US and Europe accounting for 75% share. There is a move away from the traditional MDIs towards newer, more sophisticated DPIs reflecting the increased research into powder formulations and innovations in particle engineering.[8] Capsule-based devices in particular, offer many benefits to patients in terms of precise dosing, ease of use and dose visibility. The devices are hygienic to use and simple to clean and are presented in attractive designs.

For manufacturers capsule-based DPI technology provides greater freedom to innovate and differentiate their products whilst benefiting from straightforward development, speed to market and efficiency in later manufacturing. In addition, capsule-based DPIs meet the practical requirements expressed by patients whilst ensuring effective treatment delivery.

Nowadays, the ideal development partner for capsule systems has to offer both standardized inhaled delivery solutions for smaller pharmaceutical and generic companies or more original, tailor-made solutions for larger companies.

Whether it concerns a standard or tailor-made capsule based inhalation system Capsugel assists customers with:
- Formulation and analytical development capabilities
- Customization of capsules and device selection to achieve performance targets
- Laboratory scale manufacturing
- Clinical supplies of placebos and comparators

> *"Capsugel is widely used in the pharmaceutical market: big volume, big experience!"*
> ***R&D director, Pharmaceutical company***

REFERENCES

1. Dry Powder Inhalation: Devices, Drugs, Therapeutics, Markets and Forecasts, Greystone Associates, July 2009.
2. DPI Solutions – Overall landscape and patients' expectations, Market Research Study by Vision Critical for Capsugel, April 2011.
3. Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, Crompton GK; on behalf of The Aerosol Drug Management Improvement Team (ADMIT). Retail sales of inhalation devices in European countries: So much for a global policy. Respir Med. 2011 Jul;105(7):1099-1103.
4. Heijerman H *et al*. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus J Cyst Fibros. 2009 Sep;8(5):295-315.
5. Media Releases: Novartis receives EU approval recommendation for TOBI® Podhaler®, a fast and simple therapy that helps reduce treatment burden for cystic fibrosis patients, September 2010 (http://www.novartis.com/newsroom/media-releases).
6. Newsroom: FDA Grants Bayer HealthCare Pharmaceuticals Orphan Drug Designation for Investigational Ciprofloxacin Dry Powder Inhaler for the Treatment of Cystic Fibrosis, March 2010 (http://pharma.bayer.com).
7. DPI Solutions – Overall landscape and clients' expectations, Market Research Study by Vision Critical for Capsugel, January 2011.
8. PRWeb. Global pulmonary drug delivery technologies report. March 2010.

Capsugel Library

Colmar, France
10, rue Timken
FR-68000 Colmar
T +33 3 89 20 57 09
F +33 3 89 41 48 11

Bornem, Belgium
Rijksweg 11
BE-2880 Bornem
T +32 3 890 05 11
F +32 3 889 26 22

More information? Contact us at
marketing.emea@capsugel.com or +33 3 89 20 57 25

www.capsugel.com
www.mycapsugel.eu

grey healthcare group 2011 09 001

Capsugel Library