Opportunities for capsule-based DPIs in emerging markets

This article reviews trends in dry powder inhalers and examines attitudes about inhalation devices among physicians in Turkey.

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Over the next decade, the pharmaceutical industry is expected to grow faster than the world economy, particularly in emerging countries. Due to their growing economic prosperity and aging populations, emerging countries are experiencing a decreasing proportion of acute diseases and a growing proportion of chronic diseases and conditions.[1]

Chronic respiratory diseases are a leading cause of death and disability worldwide. The prevalence and incidence of asthma and COPD, in particular, are expected to increase in the coming years. This increase in asthma and COPD cases is expected to result in concomitant gains in the respiratory treatment market, where it is anticipated sales will reach US $37.7 billion by 2016.[2] Sales may be especially robust in emerging markets, where the demand for cost-effective respiratory drug therapies is particularly pronounced.

Even in high-income countries like the US, patients can have difficulty paying for needed inhalation treatment. In 2011, the Centers for Disease Control reported that 40.3% of the uninsured could not afford to pay for asthma treatment, nor could 11.5% of insured asthma patients.[3] The unmet need is even greater in emerging markets, due to the high cost of inhalation products. Developing affordable products for these markets poses huge challenges but at the same time presents commercial opportunities for the healthcare industry.

The standard treatment for asthma and COPD is inhalation therapy, achieved mainly through the use of two types of devices: the pressurized metered dose inhaler (pMDI) and the dry powder inhaler (DPI). This article will focus on DPI devices; the features and benefits they offer patients and physicians, and the ways future trends, developments and improvements may impact the use of DPIs in rapidly-growing markets.


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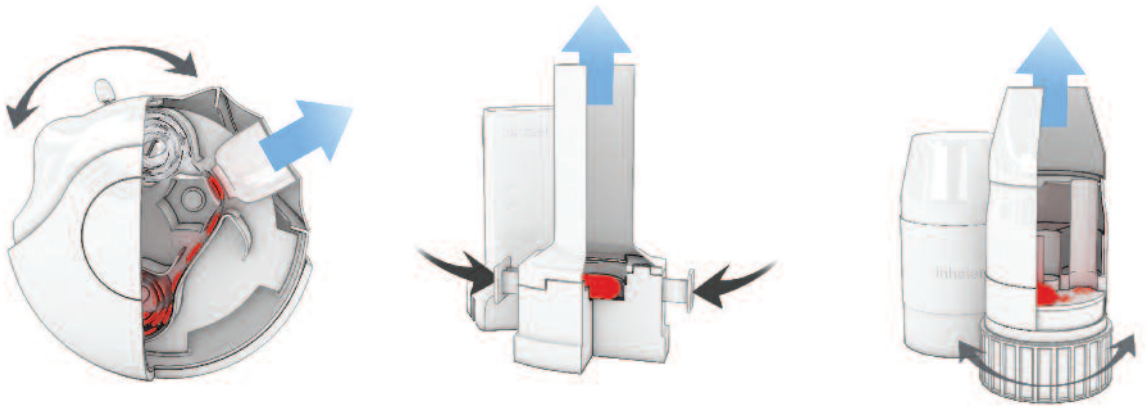
Three types of DPIs

In the early 1970s, dry powder inhalers were developed and brought to the market as pulmonary delivery systems that delivered a dose by dispersing a drug-containing powder mixture upon breathing through a device to the lung.

Dry powder inhalers (DPIs) consist of three types: capsule-based, blister-based and reservoir-based DPIs (Figure 1). All DPIs have the same three fundamental components: the interactive powder mixture, the primary packaging (capsule, blister or reservoir) and the device. The components interact with each other to deliver a precise and reproducible amount of fine drug particles to the lung.

Figure 1

The three types of dry powder inhalation devices: blister, capsule and reservoir



However, the three types of DPIs differ significantly in the way they function:

• Blister-based DPIs involve pre-metered drug doses. The doses are enclosed in foil blister disks (typically about 10 doses per disk) that are loaded into a multiple-dose device. The powder is released when the blister is pierced by a needle or when the blister foil is peeled off.

• Capsule-based DPIs are also referred to as "pre-metered" single-dose because they use two-piece capsules containing previously-measured doses of the active pharmaceutical ingredient (API) plus excipients. The capsules, made either of hard gelatin or hypromellose (hydroxypropyl methylcellulose, HPMC), are inserted into a single-dose device by the patient prior to use.

• Reservoir devices contain up to 200 doses of powder (the API plus excipients) that have been preloaded into the device's reservoir. From the reservoir, the drug plus excipient mixture is metered into cups and delivered by gravity to an inhalation passage.

DPI innovation

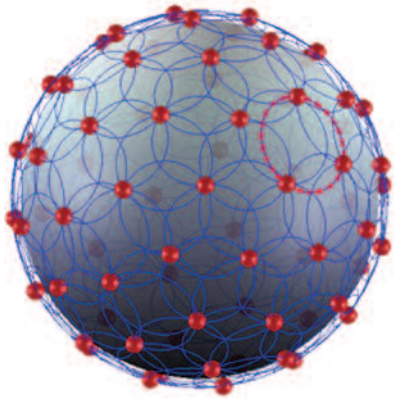
Technological advances in inhalation formulation and device design have elevated DPIs as an alternative for effectively and efficiently delivering inhalation drug therapy. The performance of DPIs is continuing to improve. A principal reason is better understanding of the dynamics of interactive powder mixtures.

Research over the past 20 years has led to key insights into the dynamic interaction among fine drug particles and carrier particles and the ways those powder mixtures interact with the device that is propelling them.[4] The goal is to segregate drug particles between one and five microns in diameter—the size best suited for reaching the lung alveolae—from the carrier particles upon breath activation and maximize drug delivery to the targeted areas of the lung epithelia.

It is known, for example, that certain characteristics of the carrier particles decisively affect the performance of DPIs. Specifically, interaction between drug and carrier particles depends on the nature of the surface where drug particles and carrier particles come in contact with each other. Manufacturers have acted on this knowledge to alter the surface roughness or smoothness of carrier particles to optimize the detachment of drug particles from carrier particles upon inhalation.[5] One of the latest and most innovative proposals in this area would create "carrier-free" formulations by coating drug particles with nanoparticles to reduce drug particle interaction[6] (Figure 2).[7]

Figure 2

A theoretical drawing of nanoparticles attached to a drug particle. The nanoparticles are intended to prevent clumping by interfering with surface interactions between particles.



Advances in particle engineering have contributed to greater efficiency in powder deposition among DPI devices. This improvement has been especially notable for capsule-based devices due to advances in capsule technology. To further enhance the efficiency of powder emission, these devices use customized capsules with precise moisture contents and capsule weights to fit the specific requirements of a given compound. They are also designed with inner capsule properties that meet requirements for powder retention, resulting in optimal delivery of specific drugs via DPIs.

Another area of research focuses on the release of the interactive powder mixture from the capsules. The drug is released from the capsule through either needle piercing or cutting of the capsule. The composition of the capsule can be adapted to achieve optimal drug release. For example, capsules containing moisture-sensitive drugs can be customized to a defined low moisture range and water activity.[5] Both types of capsules exhibit good puncturing behavior under a wide range of relative humidity conditions (33% to 80%). In addition, testing to quantify powder retention following capsule

How do DPIs rate in Turkey?

In November 2006, IMS Health coined the term "pharmerging market" in recognition of the shift in growth away from mature, developed economies towards seven countries, including Turkey, described as "fast-growing emerging economies."[9]

In late 2011, Capsugel conducted a qualitative market survey in Turkey, due to the large size of its inhalation market and a broad range of inhalation therapies, both brand name and generic, for treating asthma and COPD. This enables physicians to adapt the choice of device and molecule to suit the patient.

The survey utilized in-depth interviews with six respiratory specialists to determine their attitudes and those of their patients regarding the advantages and drawbacks of pMDIs and the three types of DPI devices (capsule-, blister- and reservoir-based). In addition, the survey sought to learn the key criteria among the specialists for optimal drug delivery and good patient compliance. The results offer insight into the ways fast-growing market demand may affect the DPI market in the decade ahead.

At the time the survey was conducted, respiratory specialists were solely responsible for examining and treating asthma and COPD patients. But under new legislation passed in 2012, such patients must now consult first with a general practitioner before being referred to a specialist. The impact of this change on respiratory therapy devices is unclear.

Respiratory specialists in Turkey report that ineffective treatment is due primarily to patient non-compliance with the inhalation system. They were generally accepting of generic versus brand inhalation devices while being skeptical of generic drugs used in devices.

The survey elicited the attitudes of respiratory specialists and their patients regarding the various types of inhalation therapies. Not surprisingly, there is no perfect device for pulmonary drug delivery. Instead, all four types of inhalation devices (pMDIs and the three types of DPIs) were found to have positive as well as negative attributes, as follows:

- The specialists have a positive image of pMDIs because they are multi-dose systems that are small enough to fit in a pocket and offer fast relief during an asthma attack.
- The main drawbacks identified for pMDIs are that patients have difficulty coordinating device activation with inhalation and are usually not able to count the number of doses remaining.
- The physicians regard capsule-based DPI devices as the most widely-used inhalation products in the country across all patient types. They note that capsule-based devices are easy to understand and administer, making them especially suitable for the majority of patients who are low-to-middle class and not well educated.
- Capsule devices make patients feel more engaged when taking their medication because they see the capsule as they insert and eject it, hear the capsule being pierced and know they should then inhale, then feel the product in their throats upon inhaling the product.
- With respect to drawbacks, capsule devices require some handling to load the capsule and administer the dose. They are also perceived as less innovative since they have been available in Turkey for many years.
- Physicians regard blister-based DPIs as especially suited to young patients because of their attractive appearance and speed of use. They also like the fact that these devices contain counters to indicate doses remaining, helping to ensure that patients will not run out of medication.
- Blister-based DPIs may not be suitable for the elderly or those with physical disabilities due to bulkiness and difficulty understanding how they should be used.
- Physicians particularly liked reservoir-based DPIs because they are used with drugs for acute treatment and long-term treatment. In addition, they are multi-dose devices that fit easily into a pocket and come with a humidity sensor that aids in proper storage.
- Drawbacks of reservoir-based DPIs include the absence of taste and therefore no proof to the patient that the drug has been inhaled, as well as a dose counter that is too small to be read by some patients and imprecise because it counts doses in fives.

piercing consistently shows that only negligible amounts of powder are retained.

The effect of these improvements becomes clear when comparing old and new capsule-based devices. The Rotahaler device (GlaxoSmithKline), for example, delivered only 6.2% of fine drug particle to the deep lung compared with such next-generation capsule devices as the Aerolizer (Novartis) (13-28%) and Flowcaps (Pantocampo) (44%). In fact, the deposition efficiency of these capsule-based DPIs now ranks with multidose reservoir-based devices including the Turbuhaler (AstraZeneca) (15-31%) and Easyhaler (Orion) (25-35%).[8]

At the same time, capsule-based DPIs are limited in that they are single-dose systems that require reloading by the patient for each application. This is in contrast to pMDIs and to blister-based and reservoir-based DPIs, which allow multiple dosing. Efforts are now underway to create a new generation of multi-dose capsule devices that would be more convenient for patients and will help to improve their compliance with treatment.

Capsule-based simplicity

Some of the key factors influencing the manufacturing cost of a DPI system are the complexity of the inhalation device, the sophistication of the primary packaging (i.e., the blister or container) and the availability of manufacturing and filling equipment to produce the product. Capsule-based inhalation systems may offer advantages over competing DPI systems when three cost factors are considered.

Complexity of the device. Single-dose, capsule-based inhalers generally cost less than other DPI systems because they consist of fewer parts. The Foradil (Astellas Pharma) device, for example, contains six parts and the Rotahaler has only two parts. Reservoir-based and blister-based DPI devices normally require more than 20 high precision plastic and metal parts that are assembled in various steps,[6] usually making the devices more expensive and potentially increasing the risk of product failure.

Sophistication of the primary packaging. The primary packaging for drugs in a capsule-based inhalation device consists of a simple two-part capsule made of either hard gelatin or hypromellose, both of which are readily available. Blister-based devices require a customized manufacturing and filling machine and mainly use aluminum as a base material. Reservoir-type devices have a custom-made design and preloading chamber that must be protected from moisture ingress.

Availability of manufacturing and filling equipment to produce product. Capsule filling is an established technology and capsule-filling machines are standard equipment in companies all over the world. The widespread availability of these machines enables companies to readily respond to local demands for increased production.

Expectations for the future

In the future, it is expected DPI devices will continue focusing on the features that have helped them become prime candidates for use, not only in emerging markets but in mature markets where drug costs are coming under scrutiny due to limited healthcare budgets. Those features include simplicity of design, ease of use and improved powder flow dynamics and lung deposition.

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