Choosing between capsules and blisters

An introduction to DPI dosage units

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Pre-metered dosing units for DPIs

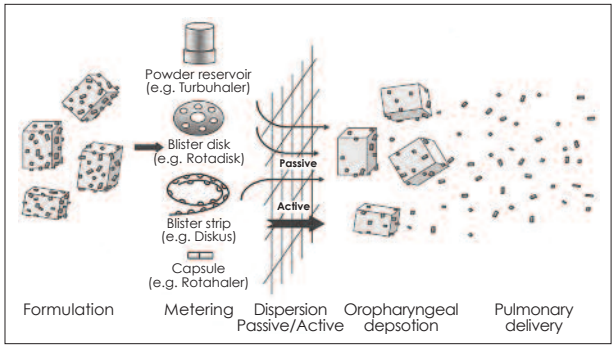
Current advances in inhalation device mechanics and design are creating new avenues for pharmaceutical companies to use inhaled drug delivery as an alternative to oral and parenteral drug delivery formulations. Several approaches for delivering active pharmaceutical ingredients (APIs) locally and systemically to the lungs are currently in use. Recent advances, investments and interest in dry powder formulations, particle coating and engineering, and device design have positioned dry powder inhalers (DPIs) to grow in the market.

DPI devices can be divided simply into device-metered DPIs and pre-metered DPIs, both of which can be driven by patient inspiration alone (passive) or with power-assistance of some type (active). Device-metered DPIs usually rely on an internal reservoir which holds the formulation that meters the dose through actuation of the device. Pre-metered DPIs contain previously-measured doses or dose fractions in some type of unit (e.g., capsules or blisters) that are usually inserted into the device by the patient before use. The differences in dosing units and dispersion are two primary principles in DPI design and are illustrated in Figure 1. These unit types have evolved over the years and enable DPI manufacturers to choose the dose unit most suitable for their device.

The two primary types of dosing units for DPIs are capsules and blisters. These dosing units are both used in marketed products for a variety of indications such as asthma, chronic obstructive pulmonary disease (COPD) and influenza. The choice of dosing unit in a DPI depends on various factors including API characteristics, required dose, interactions of the formulation with the device and other considerations. Capsules and blisters have different attributes that can lead a company to one dosing unit over the opposing type.

Figure 1

Principles of DPI design. Companies can choose among several dosing systems (metering methods), including capsules or blisters, to deliver their drug. (Image courtesy of UNC Eshelman School of Pharmacy)



Capsules

Capsules had been used in DPIs for more than 40 years when the pharmaceutical division of Fisons introduced the Spinhaler device. The device used two pins to punc-

ture a hard gelatin capsule in order to release the active pharmaceutical ingredient. One disadvantage of using a hard gelatin capsule was creation of a flap on the capsule that could either detach and be inhaled by the patient or reclose after the pins were retracted.[1] In response, formulators developed a gelatin blend that would allow a capsule to be punctured without detachment of the flap and avoid flap reclosure.

A capsule dosing unit allows accurate dosing, easy patient use and short manufacturing time. However, this familiar dosage form had a drawback as a dosing unit: it proved to have safety concerns. In 2005, the US Food and Drug Administration (FDA) issued a warning to healthcare providers about unintentional oral consumption of inhalation capsules by patients. At that time, inhalation capsule packaging did not have a warning advising patients not to consume capsules orally. The FDA subsequently worked with manufacturers to address this issue.

Other disadvantages of hard gelatin capsules, including brittleness, relatively high water content and chemical/physical interactions with ingredients, have led to the development of capsules using hypromellose instead of animal-derived gelatin. Hypermellose is a plant-based polymer, widely used in both the food and pharmaceutical industries. The properties of hypermellose and gelatin are similar but hypermellose allows for a decrease in moisture content without physical changes to the capsule. When gelatin capsules lose moisture due to storage or interactions with ingredients, the capsules can become brittle, leading to irregular punctures or cuts that can result in patient inhalation of a detached part of the capsule. According to a recent study, almost 85 percent of patients surveyed incorrectly stored their inhalation capsules and had insufficient knowledge of correct storage methods.[2] Such incorrect storage can lead to loss of moisture content as well as capsule brittleness.

Devices using inhalation capsules have also evolved in their method of releasing the formulation. Initially, inhalation capsules were punctured using pins in the Fisons Spinhaler. Later Glaxo (Allen & Hanburys) began using inhalation capsules in its device for the administration of salbutamol and beclomethasone in asthma treatment. However, the Glaxo inhaler used a blade to cut the capsule shell in half to release the ingredients. This method was further refined by the Cipla Rotahaler device, in which drug release starts when a spinning cylinder sleeve separates the top of the capsule from the capsule body.

Currently many DPIs use capsules as their dosing unit, particularly for once-daily dosing regimens. Both the Spirivia Handihaler (tiotropium bromide) from Boehringer Ingelheim (Figure 2) and the Foradil Aerolizer (formoterol fumarate) are indicated for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) and for reducing COPD exacerbations. These products only require once-daily dosing, which makes capsules an attractive choice for these products.

Blisters

While capsules are loaded into devices for each use, blisters enable multiple doses to be loaded into a device at one time, thereby offering convenience for patients.

As show in Figure 3, blisters are usually packaged in a layer of foil that provides protection from outside elements such as humidity, oxygen and UV light. Blisters also permit a longer shelf life and decreased risk of tampering and contamination.

Blisters are commonly manufactured by a cold form process from a ductile foil laminate or plastic that includes a puncturable lid. In most cases, the lid is permanently heat-sealed around the blister after the formulation is metered. During the cold form process, blisters are created by pressure rather than heat, as used in thermo form blister packing.[3]

Figure 2

The Spiriva Handihaler (Image courtesy of Boehringer Ingelheim)

Generally, a blister is punctured by actuation of a DPI. A few devices, such as the Diskhaler used in Relenza (zanamivir) from GlaxoSmithKline, require both the top and bottom of the blister to be punctured for accurate dosing. In developing a blister, manufacturers select both the hole pattern and hole size to provide optimum delivery of their particular medication. When the patient inhales, air is drawn through the blister, entraining the dose. The dose is carried out of the blister, through the device and into the patient's airway. When the patient is ready for another dose, a mechanism moves the emptied blister out of the opening and a new blister into position.

The Diskhaler device is designed to provide a small number of doses and contains eight blister packs inserted into the device on a rotating wheel. However, blister dosage capacity has evolved and now can deliver nearly eight times that number of doses. For example, the Diskus device used in products such as Flovent (fluticasone) and Advair (fluticasone and salmeterol), both from GlaxoSmithKline, can hold as many as 60 doses on its blister tape.

In order to track multiple doses, inhalers that use blisters generally have a built-in dose counting mechanism. The counter shows the patient the number of remaining doses and indicates when the medication should be replaced. A dose counter can also help avoid unintentional inhalation of multiple doses as well as over-dosing that can occur if the dispensing mechanism is actuated multiple times between consecutive patient inhalations.

As noted earlier, it is advantageous for an inhaler to hold multiple doses so it can be used repeatedly without having to open and/or insert a new blister. This is a popular option for many products such as Advair and Relenza (zanamivir), also from GlaxoSmithKline. Relenza is indicated for treatment of uncomplicated acute illness due to influenza A and B virus. Its dosing regimen is one 5 mg blister twice per day. Since the product provides four blisters per pack, this allows a patient to take multiple doses without having to insert a new blister pack. Advair is indicated for asthma and its dosing regimen is one blister twice a day. This product offers 60 blisters per pack, which is an appropriate packaging option due to the chronic nature of asthma.

Making a choice

Both capsules and blisters have evolved significantly from the time when they were first used in inhalation therapy. Capsules have changed their composite material and manner of release while blisters have increased the number of doses and have features such as dose counters.

Companies choosing the type of inhalation device and dosing unit that would be the ideal fit for their product can base their choice of capsule or blister on many factors including the patient population, therapeutic indication and amount of dosing needed.

References

1. Bell JH, Hartley PS, Cox JSG. Dry powder aerosols I: a new powder inhalation device. J Pharm Sci. 1971;60:1559-1564.

2. Renswouw DC. Storage instructions for inhalation capsules: consequences of incorrect storage and adherence in daily practice. J Pharm Pract. 2010 Dec;23(6):548-52. Epub 2010 Aug 16.

3. Soroka, W. Fundamentals of Packaging Technology. IoPP. 2002.

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Figure 3

An inhaler using blister packaging