

SELECTING A DOSAGE FORM FOR DRUG DELIVERY TO THE LUNGS

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Recipharm is frequently asked to help its clients select and develop an appropriate dosage form for their inhalation product development programs. When choosing between metered dose inhaler (MDI), dry powder inhaler (DPI) and nebulised dosage forms, a wide range of technical, business and regulatory factors are worthy of evaluation. A few of those key considerations are discussed below.

PHYSICOCHEMICAL FACTORS

Salt form screening is an important early step in inhalation dosage form selection. Approximately 50% of active pharmaceutical ingredients (APIs) in approved products are salt forms¹, and that proportion is slightly higher (~60%) for APIs in approved inhalation products. For each type of formulation (e.g. solution versus suspension) or dosage form, it is conceivable that a different salt form will be most amenable for development. As with all pharmaceutical development, understanding the physical and chemical properties of the active pharmaceutical ingredient (API), and its different forms if applicable, is critical in defining the dosage form design space.

The following API characterisation studies may be warranted based on the inhalation formulations and dosage forms under consideration:

- ▶ Polymorph screening
- ▶ Amorphous content
- ▶ Hygroscopicity and moisture content
- ▶ Surface properties
- ▶ Solubility in the formulation matrix
- ▶ Morphology and size
- ▶ Density
- ▶ Flowability
- ▶ Chemical /physical stability
- ▶ Excipient and device compatibility

MDIs and nebulised products may be formulated as solutions or suspensions. For a solution formulation, the API should be completely soluble in the formulation, with a safety margin to prevent precipitation during cold temperature excursions. For a suspension formulation, the API should be essentially insoluble in the formulation (e.g. < 0.1 ppm solubility²), otherwise crystal growth ("Ostwald ripening") may occur. Most marketed MDIs are suspensions due to the challenges of solubilising APIs in hydrofluoroalkane (HFA) formulations. If solubilised, for example with the assistance of a co-solvent such as ethanol, chemical stability can then be an issue. As an early step in MDI formulation feasibility, Recipharm can evaluate solubility of the API in HFA formulations, as well as chemical stability.

In contrast to MDIs, most nebulised products are solution formulations. But the solubility considerations for solutions and suspensions are the same as outlined above for MDIs.



For dry powder inhalers, salt selection should be made considering carrier compatibility, ease of processing and dispersion (e.g. flowability), minimising hygroscopicity and stability. The feasibility of fine particle generation (e.g. micronisation) can be another factor to consider for APIs used in dry powder or suspension formulations.

Recipharm can work within the limitations of your API to develop a plan for dosage form feasibility studies. In some cases, pre-formulation data can suggest that more than one dosage form may be feasible and a parallel path of formulation development and stability characterisation may be warranted, looking at two or three dosage forms at once. These paths may converge on one dosage form to promote to preclinical toxicology or first-in-man studies.

Setting off on the right foot with these early studies can be critical to the timeliness and ultimate success of an inhalation development program.

DOSE

The required dose can play a significant role in selection of an inhalation dosage form. MDIs, DPIs and nebulisers can each perform well in delivering very small doses in consistent fashion. The differentiation is observed in delivering high doses. MDI suspension formulations can deliver upwards of 1 to 5 mg of drug per actuation, above which the metering valves may clog or malfunction. The delivery capacity for MDI solution formulations is dictated by the solubility of the drug in the formulation and the valve metering chamber volume, which is normally in the range of 25 to 100 μ L.

DPIs can deliver much higher drug payloads, to limits of patient tolerability (e.g. as high as several hundred milligrams). Typically, dry powder formulations are comprised mostly of carrier particles, though neat drugs can sometimes be delivered effectively via particle or device engineering.

Nebulised products can also deliver high doses. For example, a 5 mL ampule of TOBI® (tobramycin solution for inhalation) is formulated with 300 mg of drug.

TARGET PATIENT POPULATION

MDIs are used over a wide range of patient populations. However, small children (e.g. less than about 4 years of age) and some geriatric patients may have difficulty coordinating their breath with the actuation of the device. In those cases, a spacer or valved holding chamber may be used to remove the need for breath coordination. Likewise, small children or patients with compromised lung function may not be able to generate the inspiratory flow required for operation of passive DPIs.

Nebulisers can be used by most patients, but the devices tend to be large and not easily transported. Another drawback of nebulisers is that treatment times are much longer than for MDIs and DPIs. Nebulisers are a common choice for hospitalised or critical care patients. Of all target populations, cystic fibrosis patients are perhaps the most accustomed to nebulised treatments, though many would welcome options that are more convenient³.



TIMELINE AND BUDGET

Of the three inhalation dosage forms, nebulised products are typically the least expensive and quickest to develop. One reason is that nebulised formulations are usually aqueous solutions and tend to be less complex than MDI and DPI formulations.

Another reason for the difference in relative costs is that MDIs and DPIs are regulated as combination products (formulation and device). A significant portion of the total development costs for MDIs and DPIs can be the extensive product characterisation studies required for the formulation with its device, such as the following:

- ▶ Priming/repriming
- ▶ Temperature cycling
- ▶ Device cleaning
- ▶ Effect of orientation
- ▶ Profiling of doses near device exhaustion

As most nebulised products are regulated separately from the device, less product characterisation is required. However, the regulatory trend may be toward regulation as combination products.^{4,5}

Device considerations can also weigh into the relative costs and timelines for development. For MDIs and nebulised products, off-the-shelf devices are readily available. However, few off-the-shelf options exist for DPIs. Developing a new DPI device or licensing a device that is still under development can add significant time and cost to a program, though the upside can be the creation of a higher barrier to entry for generic competition.

Finally, Recipharm recommends, where feasible, to start a development program with the dosage form that is intended to be marketed. While it may be quicker and less expensive to get to a Phase I clinical study with a nebulised dosage form, if the final product is expected to be an MDI or DPI, the overall program may be longer and more expensive due to reformulation and cross-over studies. However, there are often sound business reasons to take the cross-over approach, for example to reach the clinic quickly with a nebulised formulation to secure a next round of funding or a strategic partnership.

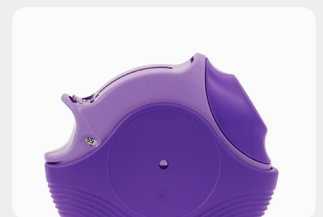
CONCLUSION

The physicochemical properties of the API, the dose, the target patient population, timeline and budget are important considerations in selecting an inhalation dosage form. Other factors, such as biopharmaceutics, intellectual property, marketing and the competitive landscape, may also be relevant. The table on the next page summarises some of the advantages and disadvantages of each inhalation dosage form, as well as device options.



NEBULISER

Aqueous solutions or suspensions administered using jet or vibrating mesh technologies that aerosolise the droplets into a fine mist.



DRY POWDER INHALER

A capsule, powder reservoir or multi-dose blister strip with passive or active deagglomeration of the drug from excipient carrier particles.



METERED DOSE INHALER

Administer medications using liquified propellants as the aerosolisation energy source.

DOSAGE FORM	ADVANTAGES	CHALLENGES	DEVICE OPTIONS
<p>Nebuliser solution or suspension</p>	<ul style="list-style-type: none"> ▶ Relatively straight-forward to formulate ▶ Could be formulated as a powder for reconstitution at time of use, if needed for shelf life ▶ For solution formulations, no need to generate fine particles of the API ▶ Can deliver low or high doses ▶ Off-the-shelf devices available ▶ Fewer product performance characterisation studies required for filing, compared to MDIs and DPIs ▶ Generally faster and less expensive to develop than MDIs and DPIs 	<ul style="list-style-type: none"> ▶ A key challenge for solution unit dose vial (UDV) formulations is solution stability of the API ▶ Proteins may lose activity upon nebulisation ▶ Devices are generally bulkier and less transportable than DPIs and MDIs ▶ Longer treatment times compared to MDIs and DPIs 	<ul style="list-style-type: none"> ▶ Jet nebulisers are widely available and inexpensive, but have large residual volumes. Shear stresses can be harsh toward large molecules.⁶ Most are not breath actuated and lose drug on the exhalation cycle. Not very portable. ▶ "Next-generation" nebulisers (e.g. ultrasonic or vibrating mesh) are more expensive, but tend to be smaller and waste less drug. Generally more portable than traditional jet nebulisers. Ultrasonic nebulisers may generate heat. Vibrating mesh nebulisers tend to be less harsh for proteins.
<p>Dry powder inhaler</p>	<ul style="list-style-type: none"> ▶ Can deliver low or high doses in single- or multi-dose configuration ▶ Avoids issues of solution stability ▶ Small and easily transported ▶ Can offer a higher barrier to entry against generic competition 	<ul style="list-style-type: none"> ▶ Physical and chemical stability can be sensitive to moisture ingress ▶ Fine powders can present challenges in processing ▶ Very few off-the-shelf device options ▶ Significant product performance characterisation studies required for filing 	<ul style="list-style-type: none"> ▶ A single-dose, capsule-based device is available "off-the-shelf" ▶ Various devices are available to license or co-develop, though few have progressed to late-stage development
<p>Metered dose inhaler</p>	<ul style="list-style-type: none"> ▶ Widely accepted dosage form with more than 50 years of market use ▶ Delivers a large number of doses in a small and easily transported device ▶ Formulations generally have low moisture content 	<ul style="list-style-type: none"> ▶ Not suitable for very high doses. Suspension formulations are generally limited to maximum doses of about 1 to 5 mg/actuation ▶ Chemical stability may be challenging to achieve in solution formulations ▶ Proteins may aggregate and lose activity in HFA formulations ▶ Significant product performance characterisation studies required for filing 	<ul style="list-style-type: none"> ▶ Cans, valves, actuators, and dose counters are widely available "off-the-shelf"

RECI PHARM CAN DEVELOP AND DELIVER A VARIETY OF INHALATION DOSAGE FORMS INCLUDING:

MDIs



MDI cannisters and valves



DPIs



Nebuliser and face mask



Nebuliser



Capsule based DPIs



ABOUT RECIPHARM

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 5000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way.

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