Developments in inhalation technology

Current developments in inhalation technology are expected to bring about a major transformation in the way that drugs are delivered to the respiratory tract.

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The link between developments in inhalation technology over the last decade and skin cancer and cataracts caused by ozone depletion may be difficult to make at first glance. The global phase-out of CFCs (chlorofluorocarbons), aimed at restoring the depleted ozone layer and hence the earth’s protective shield against the high energy UV radiation from the sun, offered a formidable challenge to the pharmaceutical industry to develop alternatives to the CFC-driven pressurised-metered dose inhaler (MDI). Few would disagree that much of the stimulus to innovative developments in the area of inhalation technology has been provided by the banning of CFCs under the terms of the Montreal Protocol announced in 1986.

During the 1980s, the majority of drugs requiring delivery to the respiratory tract for the treatment of asthma were from the pressurised-metered dose inhaler (MDI). The need to either re-formulate the MDI using non-CFC propellants, or develop alternative delivery systems, was clear by the end of the 1980s.

The primary objective of delivering drugs by the inhalation route has been to target better the drug to the required site. In order for the drug to be able to penetrate into the lung and deposit in the peripheral regions, the drug particles or droplets must be in the range, 1-5 microns. The delivery of 0.5 milligram of drug with a particle size in this range requires in excess of 30 million particles or droplets being generated as a fine inhalable cloud of drug. Traditionally, this has been achieved using a number of delivery systems:

- Pressurised metered dose inhalers,
- Dry powder inhalers, and
- Nebulisers.

Significant developments have been made in each of these delivery systems in recent years.

Pressurised metered dose inhalers

There are a number of major developments underway in MDI technology. The major emphasis still remains on the introduction of non-CFC propellants. CFC-based MDIs contain a combination of a liquefied low boiling point propellant, CFC12, and a liquefied higher boiling point propellant, CFC11 or CFC114. The combination of these propellants allows small drug particles to be well suspended in the propellants through the use of a surface-active agent (oleic acid, sorbitan trioleate or lecithin). It is believed that stable suspensions are fundamental to meeting the increasingly demanding regulatory requirements for dosing uniformity and respirable dose delivery.

The non-CFC propellants (hydrofluoroalkanes, HFA134a and HFA227) that have been demonstrated to be safe for inhalation have extremely poor solvent properties. Thus, whilst this is beneficial in preventing the dissolution of the small drug particles, it is disadvantageous in that the commonly used surface-active agents are almost totally insoluble and thus not able to provide any stabilisation of the drug particles in the suspension. There have been numerous approaches taken to overcome the problems of drug particle stability in HFA propellants; these include:

- Increasing the solvency of the HFA propellant through the addition of a co-solvent to allow use of the commonly used surface-active agents,
- Dissolving the drug in a mixture of the HFA propellant and higher concentrations of co-solvent,
- Developing new surface-active agents specifically for use with HFA propellants,
- Modifying the particle surface properties to reduce the interfacial tension between the particle surface and the liquefied HFA, and
- Particle engineering to produce more HFA propellant compatible material.
Each of the above approaches has its drawbacks. The addition of a co-solvent to increase the solubility of the surface-active agent can also lead to partial dissolution of the drug particles, which in turn gives rise to particle growth and much reduced product efficacy. Dissolving the drug in a propellant/co-solvent mixture can lead to greater problems of chemical instability of the drug substance in the dissolved state. The approach also requires the careful optimisation of the dimensions of the actuator nozzle to ensure that the discharged spray characteristics produce a “droplet” size compatible with inhalation. The development of new surface-active agents may require extensive toxicology evaluation; the extent of this will depend on the nature of the material and whether it has been demonstrated to be safe in other dosage forms, for example, in parenteral products.

There have been attempts to modify the surface characteristics of particles through surface adsorption of the surface-active agent. Other options have included the production of micron-sized particles through the use of supercritical fluid techniques.

A recent development pioneered by Alliance Pharmaceuticals in the USA has aimed to produce drug particles with a highly micro-porous structure (Figure 1); this allows the HFA propellant to diffuse into the particle surface, thereby eliminating a sharp interfacial boundary between the drug particle and the propellant. This leads to a major reduction in interfacial tension and gives highly stable suspensions. An interesting approach developed by Vectura, UK, uses a combination of a volatile and non-volatile co-solvent with HFA propellants to enable the in vitro characteristics to be matched to those of existing CFC-based products. By ensuring good in vitro equivalence, it is expected that demonstration of in vivo bio-equivalence in clinical studies will be better assured.

One of the major recognised disadvantages of MDIs is the need for the patient to coordinate the actuation of the MDI with inhalation; this is a manoeuvre that many patients find difficult to achieve. The introduction of “breath actuated” systems has provided a convenient and portable means of overcoming this particular disadvantage. The EasiBreath breath-actuated MDI from Norton Healthcare is a good example of this technology (Figure 2). There are a number of other developments in this area, and no doubt additional systems will be introduced over the next few years.

Dry powder inhalers

Dry powder inhaler (DPI) development is perhaps where the greatest activity has been focused in recent years. There has been enormous activity in the area of device developments with many tens of devices now at various stages of development. Although the proportion of DPIs versus MDIs used by patients is increasing, it is unlikely that all devices currently under development will reach commercialisation.

DPI devices fall generally into the following classes:
- Multi-dose reservoir,
- Multi-unit dose, and
- Unit dose.

The Turbuhaler (AstraZeneca) is a good example of the first category and was the first truly multi-dose DPI device developed (Figure 3); there have been many attempts to duplicate the principles behind this product. Although the device has been marketed widely for over a decade, many still regard this system as the “gold standard” for DPIs. The Turbuhaler is now widely available with a range of inhaled drugs: terbutaline sulphate, budesonide, salbutamol and formoterol. The device is capable of delivering up to 200 doses of drug, for drug dose weights in the range of a few micrograms up to 0.5 milligram which are metered
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from a reservoir of the drug, using an internal metering disc containing appropriately sized holes. The Turbuhaler is provided with a “protective sleeve” that minimises any ingress of moisture when stored under humid conditions, as moisture ingress can significantly reduce the delivery of inhalable drug. One of the strengths of the Turbuhaler system is its ability to deliver drug particles in the absence of any excipients - although in the case of the highly potent drug, formoterol, the drug is effectively diluted using “micro-fine” lactose.

More recently Glaxo Wellcome has introduced the Accuhaler (Diskus) (Figure 3) which falls into the second category. The DPI is capable of delivering 60 doses of drug contained in a double foil blister strip that is pre-filled during production of the product. In order to dispense small quantities accurately, the drug is diluted by blending with lactose of a suitable particle size, such that the weight contained in each blister is in the region of 12-13 milligrams. This device is not fitted with a “protective sleeve” as the drug doses are contained in the foil strip that is intended to prevent excess moisture ingress.

There are many examples of unit dose systems. With these systems, the drug formulation is generally contained in a gelatin capsule which is either split into two halves, or pierced with holes or slits to provide access to the drug.

Novel devices currently under development include:

• Pre-metered devices which give some “in-factory” assurance of the delivered dose from the DPI (Technohaler, ML Laboratories),
• Devices which provide a mechanism for automatic metering of the drug dose by the patient during use (Ultrahaler, Rhone-Poulenc Rorer),
• Re-usable devices which may have a cost benefit (Multi-Dose Dry Powder Inhaler, Asta Medica), and
• Disposable multi-dose DPIs which may be
more convenient for less dextrous patients (Taifun, Leiras).

All currently marketed DPIs rely on the patient’s inspiratory effort to withdraw the powder from the metering system, entrain the powder in the air-stream and “aerosolise” any aggregated drug particles such that they are small enough to penetrate and deposit in the deep airways of the lung. There are a number of new developments that are aimed at providing additional energy to either pre-aerosolise the drug or enhance the aerosolisation process during inhalation.

The Spiros DPI from Dura Pharmaceuticals is equipped with motor and impeller to create a high shear zone through which the drug formulation must pass to exit the device. Inhaler Therapeutics is developing a DPI delivery system that uses a small volume of compressed air to pre-aerosolise the drug into a holding chamber prior to inhalation. The Prohaler from Valois also uses a small volume of compressed air but, in this case, it is released during the inspiratory cycle to facilitate drug particle dispersion. A new technology is being developed by Microdose Technologies that combines the use of a piezo-electric de-aggregation system and electrostatic particle charging to facilitate the aerosolisation process.

There are several key developments underway in the formulation of drugs for delivery via the DPI. Advanced Inhalation Research is developing a technology for producing “large” low-density particles. It has been demonstrated that particles with a geometric diameter of 10 microns and a density close to or below 0.1g/cm³ have a measured aerodynamic diameter of around 2-3 microns and are thus easily able to progress to the lower airways of the lung. It has also been postulated that because of their geometric size, such particles will not be taken up by lung macrophages, hence potentially increasing bio-availability in the lung.

The porous particle technology shown in Figure 1 is also applicable in the field of DPIs and, because of their low density, should be more easily dispersed when delivered from a DPI. This technology has recently been acquired by Inhale Therapeutics, a company specialising in the delivery of proteins and peptides by the inhalation route.

The main disadvantage of diluting the drug with lactose by blending the two components is that a large proportion of the drug is bound firmly to the surface of the lactose and unable to be released during the patient’s inspiratory cycle. Two approaches to minimising this effect have been developed. The first involves the use of a “ternary” component such as L-leucine to reduce the high-energy sites on the lactose surface (Vectura, UK) and the second by the addition of micro-fine lactose to compete for the high-energy sites in preference to the drug (Boehringer Ingelheim). Delsys, USA, is reported to be developing a means of metering small quantities of drug using electrostatic technology developed originally for the coating of television screens.

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Nebulisers

Nebulisation is regarded by many as an “old” technology but, if recent developments in liquid spray delivery systems are included, then it is an inhalation route with a high innovative potential. Traditional jet nebulisers use a flow of compressed air to aerosolise an aqueous solution or suspension of drug contained in a chamber equipped with a capillary feed system for the liquid. A carefully positioned baffle to trap the large droplets allows them to be re-cycled within this chamber. Alternatively, ultrasonic nebulisers use a high frequency vibrating plate to provide the energy needed to aerosolise the liquid.

One of the principal disadvantages of jet nebulisation is that the aerosolised drug is generated continuously and, since the inspiratory cycle time only represents approximately 40 per cent of the total inspiratory/expiratory cycle time, much of the drug is wasted. The HaloLite nebuliser (Figure 4), developed by Medic-Aid, has an electronic control feedback system allowing the nebulised aerosol cloud to be generated only during the first half of the inspiratory cycle, since any drug delivered during the second half is unlikely to penetrate very far into the respiratory tract. Eliminating aerosol generation during the expiratory cycle reduces drug wastage and provides a safer environment for patient carers when potent drugs are being administered.

Other developments in liquid spray delivery devices include the use of piezo-electric atomisation (Aerogen, USA, and Microflow Engineering, Switzerland) and high-pressure micro-spray nozzle systems (Respimat, Boehringer Ingelheim, and AERx, Aradigm Corporation, USA). The Aerogen and Microflow Engineering approaches rely on the high frequency piezo vibration of a mesh containing an array of micron-sized holes through which the drug solution is driven. The Respimat approach allows liquid to be forced under high pressure from a reservoir of liquid through two eight-micron-sized nozzles, arranged such that the liquid jets impinge on each other, providing additional liquid break-up into droplets. The AERx system forces liquid contained in a small blister pack under pressure through an array of micron-sized holes. Although there are many issues yet to be resolved with each of these systems, they do offer exciting opportunities for the delivery of drug to the respiratory tract.

Conclusion

In conclusion, the pharmaceutical industry is a highly regulated industry where patient safety is paramount and, as a consequence, has been regarded
by many as rather conservative. Some of the recent developments in inhalation technology, and the progress being made by major pharmaceutical companies and smaller technology providers in this area, are clearly demonstrating this industry’s ability to embrace new technologies for the delivery of drugs. The next decade could see a major transformation in the way that drugs are delivered to the respiratory tract, and in the types of illnesses treated by this route.

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