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Active and intelligent inhaler device development

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Abstract

The dry powder inhaler, which has traditionally relied on the patient's inspiratory force to deaggregate and deliver the active agent to the target region of the lung, has been a successful delivery device for the provision of locally active agents for the treatment of conditions such as asthma and chronic obstructive pulmonary disease (COPD). However, such devices can suffer from poor delivery characteristics and/or poor reproducibility. More recently, drugs for systemic delivery and more high value compounds have been put into DPI devices. Regulatory, dosing, manufacturing and economic concerns have demanded that a more efficient and reproducible performance is achieved by these devices. Recently strategies have been put in place to produce a more efficient DPI device/formulation combination. Using one novel device as an example the paper will examine which features are important in such a device and some of the strategies required to implement these features.

All of these technological advances are invisible, and may be irrelevant, to the patient. However, their inability to use an inhaler device properly has significant implications for their therapy. Use of active device mechanisms, which reduce the dependence on patient inspiratory flow, and sensible industrial design, which give the patient the right clues to use, are important determinants of performance here.

Keywords: Dry powder inhaler; Formulation; Inspiratory force; Delivery device

1. Introduction

Traditionally drugs for inhalation have been targeted at local or topical therapy. These drugs have often had a high therapeutic index or the relationship between dose and therapeutic effect is not linear. Such is the case for inhaled steroids and cromolyn-like drugs. For some therapies it is immediately obvious to the patient when the therapy has failed and rapid titration by the patient or carer is possible (e.g. for inhaled β_2 agonist drugs). In addition the drugs used have been relatively cheap to manufacture (in comparison with some other areas of development and production). In such cases it may be regarded as acceptable that the devices used for delivery suffer from ostensibly poor delivery (in some cases less than 20% of the drug may reach the target airways in the deep lung) and poor reproducibility, as the patient will still receive a measurable beneficial response.

More recently, the lung has been proposed as a portal for systemic delivery, notably for the delivery of peptides and proteins. It is clear that for these applications 'conventional' dry powder inhaler device technology and formulation strategies are inadequate.

To reach the deep lung, which is required for systemic delivery, it is necessary for particles to be 5 μm

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or less, preferably less than 3 μm for alveolar drug delivery. Unfortunately such particles have poor handling characteristics and must be formulated to allow them to be readily manipulated into devices. These techniques involve the production of larger physical aggregates of particles or attachment onto larger 'carrier' particles. It is the disaggregation of these small active particles from the large agglomerates that lies at the heart of the inefficiency of many devices, as this is subject to variation from a number of factors.

Regulatory authorities, in particular the FDA, now require that delivery devices have high efficiency and high degrees of reproducibility. Whilst still not approaching the level of reproducibility available to other delivery routes (e.g. oral or parenteral) these standards place a premium on all aspects of device and formulation performance, and have stimulated new technologies (Newman and Busse, 2002).

2. Active devices and inactive particles

The force required to disaggregate the primary active particles from themselves or from their lactose carriers is often in excess of what the patient, particularly those with compromised lung function, can readily achieve. In other cases the force may be sufficient, but only at certain times in the respiratory cycle. Poor and/or inconsistent performance may appear inevitable under these conditions.

Recently AFM techniques have been used to elucidate the range of forces required to detach particles from carrier surfaces (Young et al., 2003a,b). A micron sized particle (Fig. 1) can be attached to an AFM cantilever and the detachment forces over a surface can be determined. Fig. 2a demonstrates the idealised conditions for an experimental perfectly flat lactose surface. Under these conditions a relatively circumscribed range of forces is required to remove particles from the surface, and this could readily be designed into a simple device.

However, a more representative situation is described in Fig. 2b, which represents the detachment forces from a commercial grade of lactose. It can be seen from this data that a wide range, across orders of magnitude, of detachment forces is required to remove all particles from a surface.

Fig. 3a and b demonstrate an additional factor which is recognised as a contributory factor to device variance, that of humidity. Whilst it is known and expected that some particles will show additional adhesion as humidity increases it is now clear that some particles, whose performance is dominated by electrostatics, show decreased adhesion as humidity increases. Overall this factor is an additional one which contributes to the large range of adhesive forces within an inhaler formulation with which a device may have to cope.

Fig. 4a demonstrates the challenge of efficient formulation for DPI. The force available to disaggregate particles cannot readily be provided by the inspiratory force of the patient. In addition this factor is variable due to inter and intra patient variability (and, it would appear, their surrounding environment).

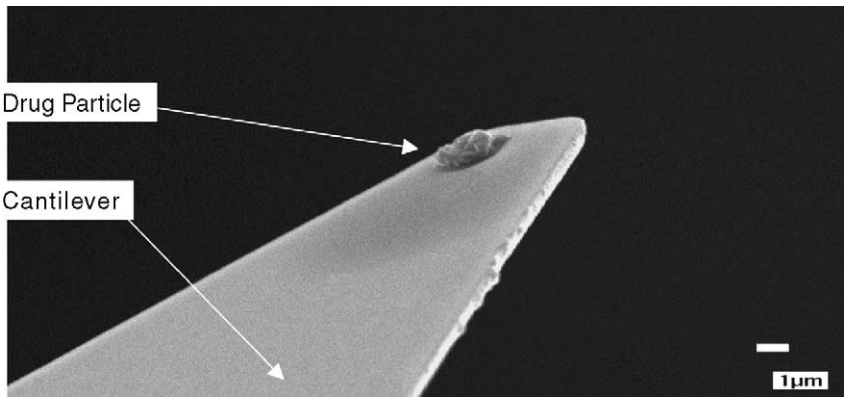

Fig. 1. Micronised drug particle on an AFM cantilever. Copyright Dr. Rob Price and Dr. Paul Young, with permission.

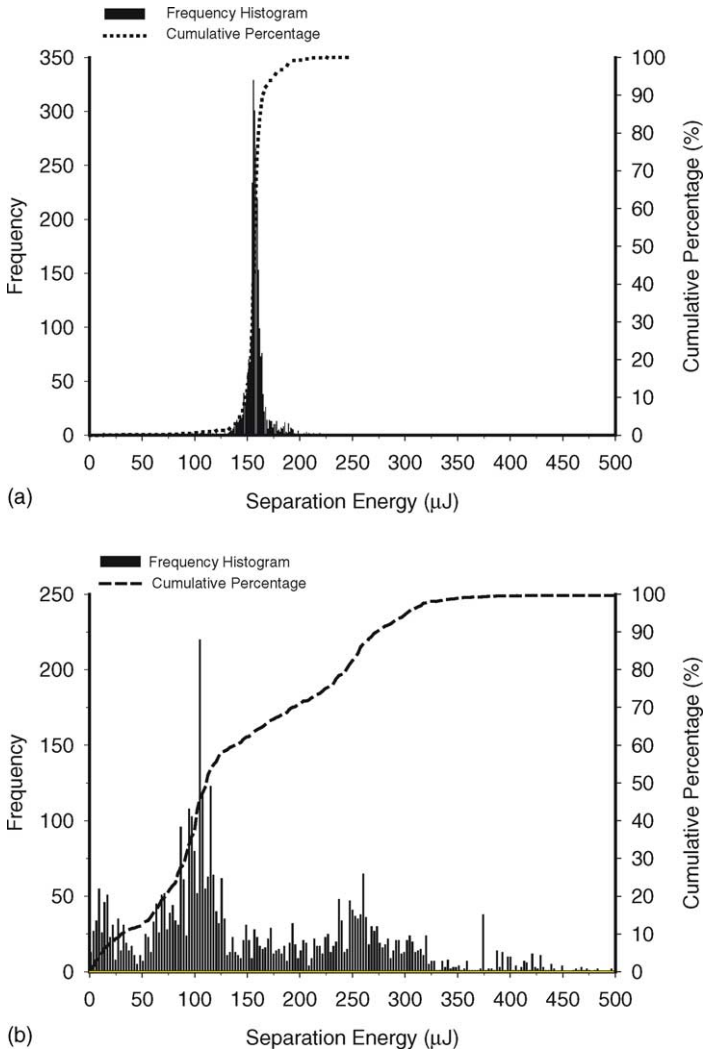

Fig. 2. (a) AFM data showing separation energies of a micronised particle from an ideal (flat) surface. Designing an inhaler to cope with this narrow range of energies would be readily achievable. (b) AFM detachment forces from a 'real' (lactose) surface. The device must be capable of maintaining the attachment of 'loose' particles during transport but must have the energy to detach a wide range of particles with varying attachment forces. This inhaler is much more difficult to design. Reproduced with permission of Virginia Commonwealth University.

Fig. 4b demonstrates one approach to reducing the variability, that is by reducing the range of forces with which the device has to cope.

It is known that micronised particles have a high surface energy, partly due to their high surface area to volume ratio (which cannot be readily changed) but also because the high energy milling required adds to the surface energy and electrostatic behaviour. This is partly because milling produces amorphous regions in contact with the crystalline regions on the particle surface, setting up potential differences.

A number of techniques have been reported to reduce the surface energy of such particles, making them less adhesive to carrier particles, themselves and to inhaler device components.

Successful strategies have included spray drying, which can produce particles with a lower surface energy than micronisation. Spraying processes can be adapted further to produce low density particles

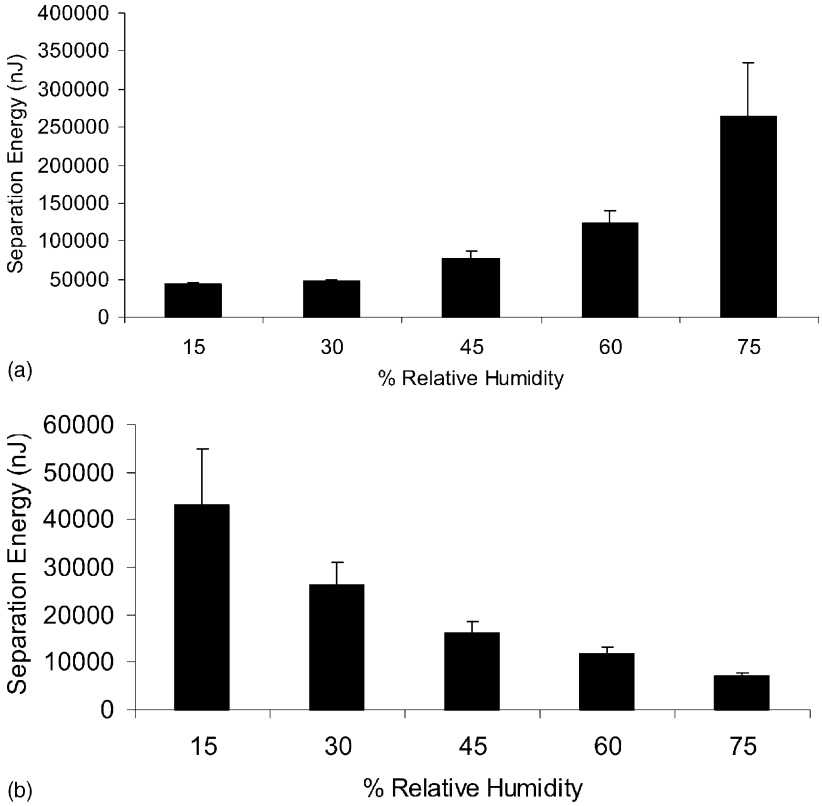

Fig. 3. (a) Influence of humidity on the adhesion of salbutamol sulphate particles. (b) Influence of humidity on the adhesion of an inhaled steroid drug. Copyright Dr. Rob Price and Dr. Paul Young, with permission.

which may have advantageous inhalation characteristics (Duddu et al., 2002).

Supercritical fluid processing has also received significant attention. This technique can produce highly crystalline (bulk and surface) materials with a controlled particle size and morphology (York, 1999).

More recently it has been shown to be possible to passivate the surface of micronised drug particles by utilising force control agents (FCAs). The FCAs can be physically bonded to the micronised particles by use of mechanofusion or other high energy techniques. Modification of the carrier particle surface by such techniques can also be demonstrated to have a beneficial effect on device performance.

A range of these FCAs, in addition to fine particle lactose, have shown beneficial properties in this field. Magnesium stearate is particularly successful in this regard. It is available in formulations in Europe and will also be launched in a formulation in the US soon. Other tablet lubricants, such as leucine, have also shown some success. The ability of FCAs to reduce and regularise drug–carrier interactions may be due to the ability to block or passivate particularly 'active' sites on the carrier surface, or due to bonding with the drug particles, independent of the carrier or as a combination of both phenomena (Clarke et al., 2002; Lucas et al., 1998; Staniforth, 1995).

One key limitation on the use of FCA's, and indeed the use of a range of agents as adjuvants (e.g. for flavouring inhalers) is the requirement for extensive preclinical work on these excipients prior to clinical trials. This will restrict the number and form of these agents available to the formulator.

Fig. 4c elucidates another approach to improving performance and reproducibility, that of increasing the amount of energy available to the device.

This involves engineering the device to put in more energy into the disaggregation process. There is clearly

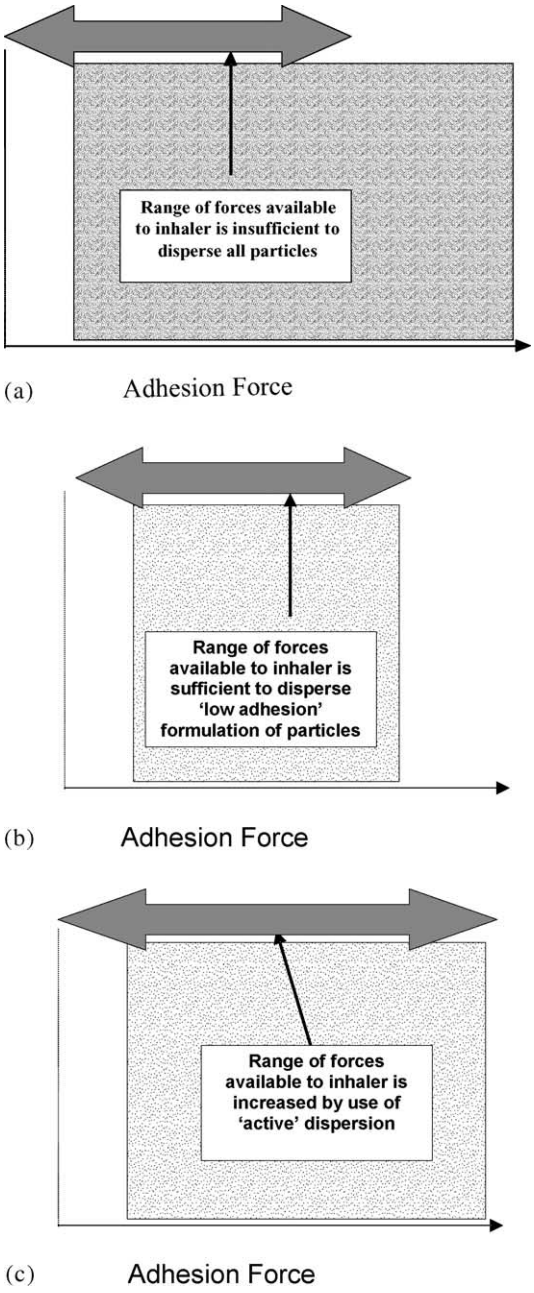

Fig. 4. (a) Range of adhesion forces necessary to detach/de-aggregate all particles is insufficient. (b) Performance improvement can be made by reducing adhesion force of particles. (c) Improving performance by increasing the energy put into the system via an active device.

a limit to how much energy a patient can put into the inspiratory manoeuvre, especially if the lung is compromised by disease. Fig. 4c illustrates this approach.

Several mechanisms have been tested which increase the disaggregation force available to the device (Newman and Busse, 2002). Some involve the use of compressed air, for instance in Nektar's Inhance device, with the patient providing the pump energy. Others (e.g. the Dura Spiros device) adopt an independent mechanised energy source provided by batteries. Other mechanisms such as piezoelectric vibration of particles have been examined.

Such active device strategies have yet to reach the market, although 'Exubera', an inhaled insulin preparation in the Inhance device is ready for regulatory submission and may launch relatively soon. This may be partly because of an aversion on the part of regulatory organisations to the notion of active devices, which need to be shown to be 'failure proof'. This seems particularly prevalent in the case of devices where the energy is provided from a stored energy source such as a battery, rather than put in by the patient. In other cases the complexity (and thus cost) of such devices makes their widespread use prohibitive.

As with any DPI system it is critical that the device is combined with a formulation technology which allows the disaggregation forces in the device to be matched with the particle attachment forces. Thus, a combination of the approaches demonstrated in Fig. 4b and c should approach the level of greatest efficiency.

3. Setting and delivering the specification for a new delivery platform

The Aspirair^{TM} device (schematic diagram, Fig. 5), currently under development at Vectura, is a novel dry powder inhaler drug delivery device, designed primarily for use in systemic conditions and for conditions where the inspiratory power of the patient cannot be relied upon. It can be combined with proven formulation approaches to produce highly efficient inhaled systems for local or systemic delivery.

In addition it aims to take account of the widely varying patient inspiratory force available from 'healthy' lungs (e.g. for systemic delivery of compounds) and that from patients whose lung function is considerably compromised (such as those that might

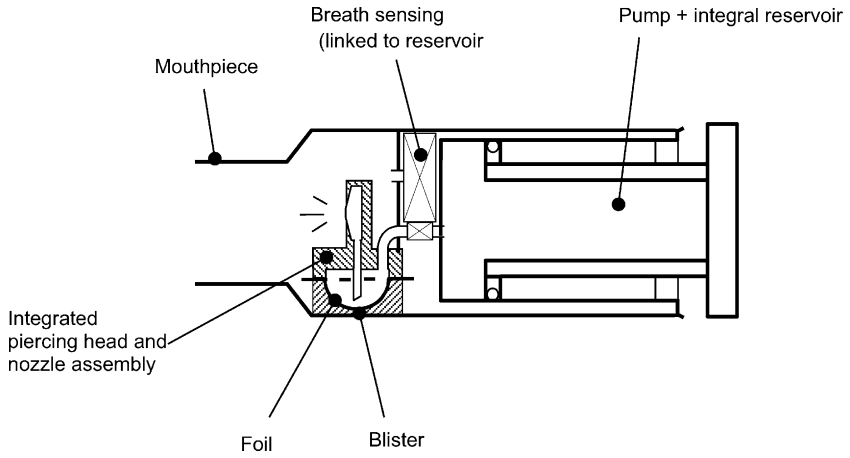

Fig. 5. Schematic representation of the Aspirair device.

pertain in cystic fibrosis or COPD patients). Fig. 6 demonstrates the approach of matching the inspiratory profile to delivery, thus maximising the opportunity for deep lung delivery.

The device uses compressed air and a novel vortex design to provide large amounts of directed energy to the disaggregation and delivery process. The compressed air is provided via a reservoir charged by the patient.

By putting in additional energy and releasing the cloud at the most appropriate point in the inspiratory cycle high efficiency delivery can be achieved.

The ideal approach is to combine an active approach with an appropriate formulation technology so that both aspects of performance are managed. For instance the Exubera delivery system utilises the active Inhance device with low cohesion spray dried particle technology.

Recent evidence has demonstrated that the techniques which lead to the greatest success in delivery from passive devices are not necessarily those which are most efficient in active devices. Having a portfolio of such approaches available is necessary for efficient delivery for a range of systems, e.g. for targeting mid range airways for asthma or the deep lung for systemic delivery. A different combination of approaches again may be necessary where the function of the lung is severely compromised, such as in COPD.

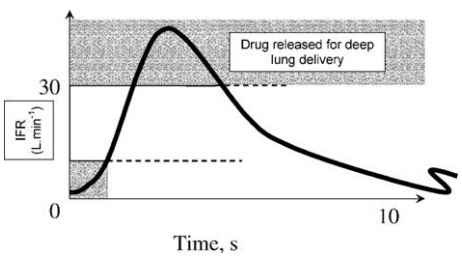

Fig. 6. Matching inspiratory flow rate (IFR) to drug release from the device optimises deep lung delivery in the Aspirair device.

The first clinical data from an Aspirair device demonstrates the advantages of an active device approach, when combined with the appropriate formulation technology, for the delivery of systemic agents.

Apomorphine hydrochloride, a treatment for Parkinson's disease, is recognised as an effective treatment for male erectile dysfunction (MED). Due to extensive first pass metabolism it is not suitable for oral drug delivery and alternative presentations have been developed, with the sublingual route marketed as Uprima. However, this route suffers from relatively slow onset of action (in a condition where spontaneity is important) and the side-effect profile prevents the clinical utilisation of those dosages demonstrated to be most effective.

Vectura have recently developed an Aspirair-based apomorphine hydrochloride formulation which optimised both the fine particle ($<5\,\mu m$) and ultrafine particle ($<3\,\mu m$) dose. The latter is thought to be important in determining the delivery to the alveoli, required for systemic delivery.

In a placebo controlled trial it was demonstrated that a 400 μg or 800 μg dose of apomorphine hydrochlo-

ride led to statistically significant improvements in erectile performance in patients with erectile dysfunction. The median onset of action for effective doses was less than 10 min, but onset as rapid as 3 min was also demonstrated.

This demonstrates that the goals of inhalation drug delivery, of fast onset of action combined with a low incidence of side-effects, can be reached by use of active devices in combination with suitable formulations.

4. Manufacturer and patient intelligence

Despite all the factors outlined above the most variable element in any device/formulation combination is the patient and/or their carer (a significant proportion of these devices will be used by parents, nurses or people other than the patient), who may be asked to operate it (McAughey, 1997).

Recent evidence has indicated that the delivery device for Relenza (Diggory et al., 2001), a novel treatment for flu, could not be operated by the patient group, the elderly, most likely to benefit from its use (which was the only group whose use of the drug was initially reimbursed by the British Health Service).

Guidance from the FDA and European Community has indicated that, in addition to carrying studies of active moieties on children, drug companies must develop dosage forms appropriate for children (FDA, 2004; EEC, 2004).

How will these factors influence inhaler design? Recently the 'e-medic' consortium, funded by the EPSRC, has taken some steps towards integrating patient and 'intelligent' device design (E-medic, 2004). However, the complexity of all the factors outlined above makes the process a highly challenging one, which will not readily be solved by a single group or consortium, and may require industry wide effort.

Patient use studies, which form an integral part of any inhaler development programme, will now have to take place in a much larger range of representative groups to ensure that the development is appropriate. These may form part of submission documents to regulatory agencies.

5. Conclusion

An active device reduces dependence on the user's inspiratory effort while appropriate formulation technologies help facilitate efficient and consistent dispersion and delivery to the target area in the lung. Integrated together, an active device and formulation combination offers a powerful and promising approach to minimising patient to patient variation and improving efficacy of delivery across the full range of patient groups.

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