

Aspects of therapeutic delivery via respiratory rate

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ABSTRACT

The investigation purposes at refining the treatment of severe respiratory diseases by delivering drugs by developing formulation strategies to enhance their local efficacy. Sincere restrictions associated with the conventional disease management of various diseases upward consideration has to be given to the development of embattled drug delivery approach. Pulmonary route of drug delivery gaining much importance in the present day research field as it enables to target the drug delivery directly to lung both for local and systemic treatment. In This review we discussed about the method and topics covering all the aspects discussed in with respect to approaches for conventional and improved pulmonary delivery of therapeutics. Hence, the better understanding of complexes and challenges facing the development of pulmonary drug delivery system offer an opportunity to the pharmaceutical scientist in minimizing the clinical and technical gaps. © 2014 Trade Science Inc. - INDIA

KEYWORDS

Respiratory;
Desease;
Embattled;
Conventional;
Therapeutics.

INTRODUCTION

The drug conveyance skill market is widely distributed or it can aid that classified on the basis of route of administration i.e. via oral, transdermal, injectable, ocular, nasal, topical, pulmonary, implantable, and transmucosal Route. Emergent consideration has been given to the impendment of pulmonary route as a non-invasive administration for systemic delivery of therapeutics mainly due to the fact that the lungs could provide a large absorptive surface area and good blood supply. Current developments with respect to conveying drugs via this route shows great promise against complication of the anatomic structure of the human respiratory system and the effect of nature exerted by the process^[1]. Influencing and controlling behaviour of the pulmonary devices is a demanding but essential el-

ement of pharmaceutical manufacturing. The development and production of inhalers demonstrates the complications confronted, by the industry with its toughest engineering challenge. Fine by necessity, to ensure deposition in the lung, formulations tend to be highly cohesive and difficult to handle^[2-4]. The need to understand the aerosolisation processes that ensure successful drug delivery adds an additional and substantial layer of complexity. Over many decades the pharmaceutical industry has developed a number of testing methods for the inhalable medicines. While these techniques have a place in describing behaviour they do not, in isolation, provide sufficient information for today's formulator. It is reasonable to suggest that the optimal analytical toolkit for dry powder applications is still being assembled. This paper examines the use of dynamic powder characterisation, in combination with shear and bulk

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property measurement, in the development of formulations. Addressing issues associated both with delivery of the dose and manufacture of the pulmonary product, it highlights how universal testers that incorporate all three methodologies have a significant role to play in supporting the advancement of this important technology^[6].

RESPIRATORY SYSTEM

The human respiratory scheme is a complex system of very close structural functional relationships. The system consisted of two regions: the conducting airway and the respiratory region. The airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs^[1,4,7].

FORMULATIONS

The drugs can be administered by pulmonary route utilizing two techniques: aerosol inhalation as intranasal applications and intratracheal instillation. By applying aerosol technique, we could achieve more uniform distribution with greater extent of penetration into the peripheral or the alveolar region of the lung, but this costs more and also faced with difficulty in measuring the exact dose inside the lungs. In contrary to this, instillation process is much simple, not expensive and has non-uniform distribution of drugs^[8-11].

AEROSOLS

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller particles get their way into the peripheral region of the lungs by following diffusion. Although there is similarity in drug absorption from the lungs and the other mucosal surfaces, but due to the complexity in aero-

sol-particle disposition, the aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract^[11]. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles. There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered-dose inhaler (MDI), and dry-powder inhaler (DPI). The metered-dose inhalers are most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs^[12]. Recently, a number of add-a-device or also called as spacers are added to use with MDIs, in order to remove some non-respirable particles by impaction on their walls and valves. 3M Drug Delivery Systems has recently introduced actuators that will make pulmonary and nasal MDIs more effective and efficient by increasing the respirable fraction of the drug delivered. This will also reduce the side effects^[13].

DRY POWDER INHALERS

The performance characterisation of dry powder inhalers (DPI) recognises the importance of three factors: the device, the formulation and the patient. Successful product development demands an understanding of how each of these shapes drug delivery, and how to test the product in a relevant way. To enable what would otherwise be impractical, invasive and potentially dangerous testing, and to remove the huge variation and costs associated with human subjects^[15], it is common practice to test inhalation devices and formulations using in vitro test apparatus. One contender for inclusion is dynamic powder characterisation using a powder rheometer. This approach is unique in its ability to measure a powder's response to air directly - an intuitively relevant characteristic for DPI design. Researchers working at the cutting edge of DPI development have reported strong correlations between dynamic parameters and the success of drug delivery, confirming the potential of the technique^[1]. Industry stan-

standard test conditions and relevant parameters have been devised and published by the regulatory authorities and within the pharmacopoeias to enable accurate comparisons between data sets^[16]. For dry powder inhalers (DPIs) performance is a function of the applied breathing profile and this is reflected in the developed methodologies. However, while standardised protocols are an essential aspect of efficient research and routine equivalency testing, the recommended representative inhalation profile does not attempt to accurately reflect performance across the entire patient population^[17].

FORMULATING DPIS

One of the advantages of the inhaled drug delivery route is that it avoids the aggressive acidity and enzyme activity of the stomach allowing the delivery of more delicate drug entities. Many therapies will simply not work if ingested and others may be far less clinically effective. Active pharmaceutical ingredients (APIs) bound for inhaled drug delivery are fine by necessity; larger particles will be ingested. Successful aerosolisation and inhalation of the DPI dose and the efficiency of API delivery are therefore inextricably linked^[18-22].

However, with particles this fine, inter-particulate forces of attraction are usually high, positioning such materials at the 'sticky' end of the cohesivity spectrum. Such powders do not flow easily and have a tendency to agglomerate. This behaviour not only makes aerosolisation problematic but also creates difficulties in production^[23].

A defining step in the manufacture of DPIs is the extraction of a suitable sized dose from a bulk mass of formulation. Inhaled drug doses are usually small, as little as 0.5 mg, 0.1 to 1% of the size of a typical tablet. The absolute tolerances on dosing are therefore exacting. Poor powder flow behaviour makes it both harder to develop a filling solution that meets the necessary consistency targets and can result in problematic adhesion of the powder to the processing equipment^[22-25].

DPI formulators have several established techniques for managing cohesion with the intention of improving aerosolisation behaviour and easing the difficulties of manufacture. Although the number of formulating ingredients approved for DPI use is far more limited than

for tablets (restricting development opportunities) certain approaches have already proven beneficial and there is considerable ongoing research activity in this area^[25].

One common strategy is to attach the API to a larger carrier particle; typically lactose. Aerosolisation of the dose then becomes a matter of stripping the active from the carrier, rather than de-aggregating the active. Research indicates that tailoring the particle size distribution of the excipient, most notably through the additions of fines to the carrier, enhances aerosolisation in such systems producing a higher FPD^[25-29]. A carrier/API blend may also be better suited to manufacture, although it brings with it the necessity of ensuring a consistently homogeneous feed through appropriate, well-controlled blending^[27].

An alternative strategy is to modify the active particles themselves to formulate a carrier-free product. Progress in this area has been achieved through, for example, the application and optimization of spray drying processes to produce active particles with closely controlled properties^[3,4] and the mechanofusion of coatings on to the surface of the active to reduce inter-particulate forces of attraction^[5]. Both these methods, and indeed other DPI formulation strategies, demand the sophisticated manipulation of particle and powder properties^[26].

HOW DO DPIS WORK?

By understanding how DPIs operate, it is possible to more closely define the characterisation data needed for development. For many DPIs, the dose is confined as a small plug of powder, typically within a capsule or blister, which is punctured immediately prior to actuation of the device. Most DPIs are classified as passive, which means that the energy for drug delivery is supplied solely by the inhalation action of the user. Dry powder inhaler users are advised to inhale strongly and deeply. As they do so, air is drawn through the powder plug which becomes aerated and ultimately aerosolises. Because the lungs are designed to filter out potentially hazardous material in the incoming airstream the particle size of the delivered drug must be very fine. Typically an upper size limit of five microns is used as the cut-

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off for pulmonary delivery. Fine particle fraction or dose (FPF/D) quantifies the amount of material (typically in the sub-five micron range) that would be expected to reach the target site within the lung and is used as an *in vitro* indicator of drug delivery efficiency^[27-29].

THE MECHANISMS OF DRY POWDER AEROSOLISATION

Various theories, based on effects at the particulate level, have been expounded to explain why the inclusion of fines enhances FPD^[6,7]. A less well-examined explanation is that enhanced drug delivery may be associated with the bulk effect of greater cohesion in the bed. A DPI dose can be treated in the same way as any other packed bed which means that the pressure drop that develops across it, as air flows, can be described using the relationship developed by Carman^[8]. This relationship, which holds up to the point of fluidisation, states that the induced pressure drop is proportional to the velocity of the flowing fluid; as velocity increases, the pressure drop across the bed rises. This is the situation in the first few milliseconds of drug delivery as the patient begins to inhale, and velocity ramps up rapidly from zero. Imagine a powder bed with no inter-particle forces. In this case, once the pressure drop across the bed is sufficient to offset its weight then particles will begin to lift beginning the process of fluidisation. This is the point of incipient fluidisation and the velocity at which it occurs is referred to as the minimum fluidisation velocity (MFV)^[30-36].

AN INHALATION THERAPY MODEL

There are three main factors involved in the most basic model of an inhalation therapy: the formulation containing the active pharmaceutical ingredient (API); the device used to deliver it; and the patient receiving it. Each of these plays an active role in consistent, efficacious treatment. In the case of dry powder inhalers (DPIs), potential particle cohesion and compaction issues caused by a high humidity environment must also be considered. With DPIs the patient, device and formulation must consistently combine to successfully

aerosolise the dose, delivering particles containing active pharmaceutical ingredient (API) in the correct size range for optimal *in vivo* deposition and absorption. Only particles below approximately five microns are considered likely to get beyond a patient's pharynx during inhalation and subsequently deposit in the lung. The percentage of these fine particles relative to the total number of aerosolised particles delivered to the patient - the fine particle fraction (FPF) - is therefore a critical measure during *in vitro* inhalation testing. An understanding of how formulation properties, device design and patient compliance and capabilities impact FPF, and other key parameters, is crucial for effective DPI development and testing^[37-41].

THE DEVICE

Dry powder inhalers (DPI) may be used to deliver both locally-acting and systemic drugs. They are often classified into two types: pre-metered or single dose systems that use capsules, or blister packs, to predetermine the amount of medication available with each inhalation, and reservoir or device-metered, multi-dose systems where a mechanism within the device itself is used to measure out each dose. Most devices are defined as passive which means that patient inhalation draws the dose from the device and into the lungs; the strength of the breathing manoeuvre providing the only motive force for aerosolisation and delivery. One of the main advantages of DPI technology is the automatic coordination of dose delivery with inhalation and the removal of any need for a propellant. In general, this makes them easier to use than a metered dose inhaler (MDI) and less likely to cause irritable side effects due to additives^(2,3). In addition, DPIs offer better sterility and stability, and play to the strengths of an industry already fluent in dry powder formulation science. Following the Montreal Protocol's progressive phasing out of the chlorofluorocarbons (CFCs) used in propellants, propellant-free DPI delivery can offer a better alternative than reformulation for a metered dose inhaler (MDI) using hydrofluoroalkanes (HFAs) or other alternatives. However, because DPIs rely on inspiratory

effort to deliver active pharmaceutical ingredient (API), in some cases their use can be limited. Effort dependent drug delivery has the potential for poor repeatability⁴ especially in weaker patients, and training is required to ensure an effective and repeatable inhalation technique. It is important to recognise that the resistance to flow that a DPI device presents is a function of its design. The air flow that a patient, inhaling with consistent strength, can generate through a DPI will therefore vary from device to device^[42-45]. A high resistance device will be associated with much lower air flows than one that presents much less resistance. Testing under representative conditions is essential to ensure that the flow rate induced by the patient's inhalation strength will adequately aerosolise a given formulation.

THE FORMULATION

Usually a DPI formulation consists of API and excipients, such as lactose. Ideally it would be API alone but because particle/particle interactions increase with decreasing size it is often not feasible to process, de-aggregate and aerosolise the typically fine API powder. To get around this, formulators use larger excipient particles as carriers^[46]. These carrier particles make the product easier to manufacture and handle, but must be stripped away from the dosage during aerosolisation, returning the API to its primary particle size for deposition in the lung. A formulation will be compatible with a given device if the flow rate the patient can generate during inhalation de-aggregates the powder bed with sufficient energy^[47] to disperse the dose. Manipulation of the physical properties of the formulation is one way of achieving this goal, changing to a device with different flow resistance properties (e.g. shear forces) is an alternative.

STANDARD TEST CONDITIONS

In a standard test set-up for measuring the aerodynamic particle size of DPI aerosols, a patient's inspiration is replicated in vitro, as far as possible within the constraints of the technology, using a vacuum pump connected to a critical flow control-

ler. A cascade impactor is used as an aerodynamic size fractionator for the delivered particles. Whilst broadly representative of lung deposition it is important to recognise that a cascade impactor is not a lung model, since particle deposition in the lungs is a function of a number of complex factors, such as sedimentation and diffusion as well as impaction⁶. The same test set-up using a particle collection tube in place of the cascade impactor is used to determine DDU^[48-51]. Cascade impaction uses particle inertia to split the delivered dose into size fractions which are then analysed to generate an aerodynamic particle size distribution for the API. The flow rate and test time used are derived represent the strength and inhaled volume of a typical patient's inspiration; the method removing variables associated with the "patient". Standard test conditions based upon the flow profile of a typical adult have been agreed industry wide and published in pharmacopoeias and are widely used by manufacturers. Cascade impactors used for inhaled product testing are constant flow rate devices, therefore requiring the production of a square-waved flow, rather than the approximate bell-shaped curve produced by a human breath profile. A control valve is used to adjust the flow to give a 4kPa pressure drop over the device, as stipulated by the pharmacopoeias. The device is then replaced by a flow meter to determine the flow rate for all subsequent testing. As shown, each device has a unique pressure drop / flow rate relationship influenced by its design. Low resistance DPIs can give very high flow rates and so the pharmacopoeias state an upper limit of 100 L/min. They also specify a total air volume of 4L for testing - although FDA guidelines set this at 2L, believing it to be more representative of a patient's forced inspiration volume. From the measured flow rate and specified air volume, test duration can be calculated. These pre-determined test conditions then apply for both DDU and aerodynamic particle size measurement testing. Flow rate stability is critical for aerodynamic particle size measurements using a cascade impactor as the equipment's performance is itself dependent on air flow. The impact of fluctuations caused by variations in pump performance must be eliminated. This is done by ensuring that the pressure down-

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stream of the flow control valve is less than half of the upstream pressure (P3) giving a critical (sonic) flow condition across the valve.

CHOOSING POWDER CHARACTERISATION TECHNIQUES

Relevant analytical tools underpin the innovation of new formulation/device combinations that permit better drug delivery efficiency, and ensure that the resulting formulations can be manufactured profitably to the required quality standards. There remains considerable debate about which tools are most suitable. The need to closely engineer the properties of the particles focuses interest on techniques that characterise individual particles and the interactive forces between them. Such analysis can yield useful insight but it is beyond current capabilities to directly predict the dispersive performance of a DPI from the resulting data. A pragmatic alternative is to investigate the behaviour of the powder Powder characterisation for inhaled drug delivery. Bulk; how the dose, in its entirety, aerosolises and how the formulation flows. It is here that dynamic powder characterisation (powder rheology) has a contribution to make. Dynamic powder characterisation involves measurement of the powder in motion. Measuring the axial and rotational forces acting on a blade as it rotates down through a sample, in a prescribed pattern, determines the baseline dynamic parameter of Basic Flowability Energy (BFE). Automated powder rheometers apply well-defined methodologies to produce highly reproducible BFE data and so the parameter is highly differentiating^[51]. It is sensitive to differences in a powder sample that are undetectable by other analytical techniques such as shear testing. For those interested specifically in aerosolisation, however, the sensitive differentiation afforded by BFE is not the most interesting aspect of powder rheology, rather it is the opportunity to measure the powder as it becomes aerated and fluidised. By measuring changes in flow energy as air flows through the sample at a known velocity, it is possible to characterise and compare the impact of air on different formulations. As air velocity through a sample is increased, flow energy falls from

the BFE value to a lower steady level. This point defines the Aerated Energy (AE) of the sample. Aeration Ratio is the ratio of BFE to Aerated Energy, an indicator of the change induced by the flowing air. Powders with low values of AE are considered to have fluidized^[52]. contrasts typical aeration test profiles for more and less cohesive powders. Non-cohesive materials tend to have a relatively high BFE that falls rapidly with increasing air velocity. Because inter-particulate forces of attraction are low, air can easily pass between each and every particle, reducing the interactive forces of mechanical frictional and particle interlocking, resulting in a powder bed where little energy is required to establish flow. In contrast, more cohesive materials have higher inter-particulate forces that resist the passage of air. This resistance tends to inhibit uniform air flow through the bed, instead inducing channelling; air finds a passage up through discrete pathways in the bed rather than uniformly fluidising the entire sample. Samples that are more cohesive therefore tend to be less affected by air, and always exhibit a higher aerated flow energy than less cohesive materials. DPI research^[1] has shown that aeration testing precisely characterises cohesion in a way that enables the prediction of likely aerosolisation behaviour. Powder characterisation for inhaled drug delivery^[53].

TEST EQUIPMENT

Inhalation test equipment from Copley Scientific measure and record all the parameters required for determining air flow rate and maintaining constant, stable test conditions in accordance with pharmacopoeia recommendations. Shows a typical equipment set-up for DPI testing and includes a High Capacity Pump Model HCP5, a Critical Flow Controller TPK 2000 and an Andersen Cascade Impactor (ACI) with throat. An alternative impactor is the Next Generation Impactor (NGI) which is widely used throughout the pharmaceutical industry. The DPI being tested is connected to the inlet of the right-angled induction port (throat) with a mouthpiece adaptor. Particles greater than around 10 microns in diameter are removed from the aerosol cloud by a pre-separator placed between the induction port

and the impactor inlet. Sample deposits are collected from each stage of the cascade impactor and analysed using high pressure liquid chromatography (HPLC)^[50-52].

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